VOLUME 102 • DECEMBER 1958 • NUMBER 6

A.M.A. ARCHIVES OF

INTERNAL MEDICINE

INDEX NUMBER

Papers Presented in the Section on Experimental Medicine and Therapeutics and on Internal Medicine at the 107th Annual Meeting of the American Medical Association, San Francisco, June, 1958

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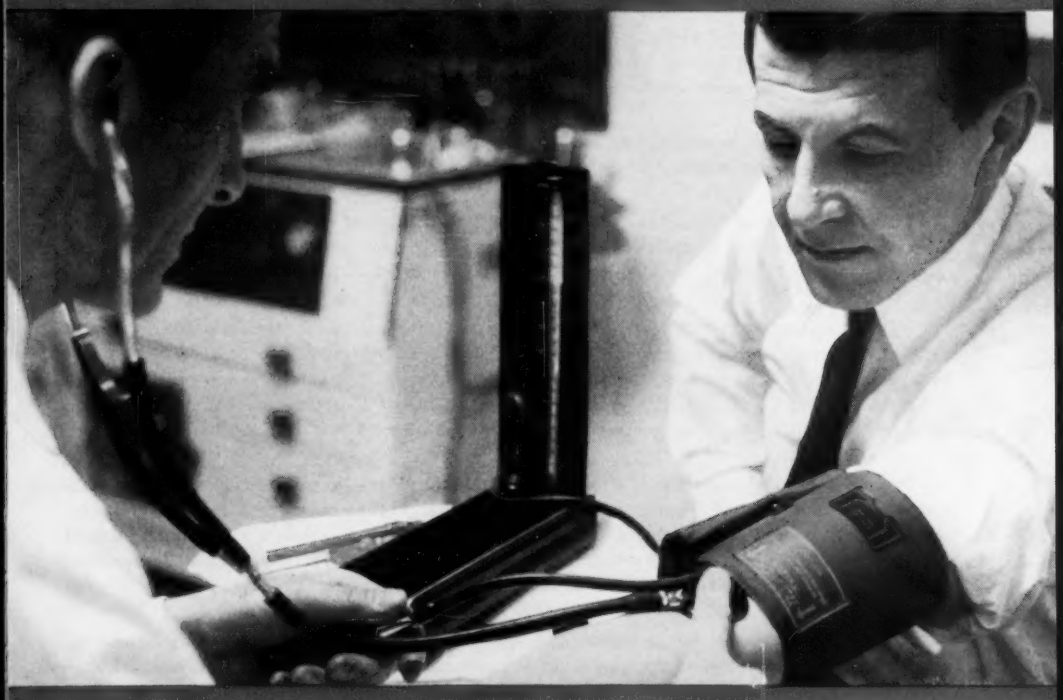

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Literature and samples on request

1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. **234**: 150, Aug. 1957.

The original meprobamate, discovered and introduced by WALLACE LABORATORIES, *New Brunswick, N. J.*

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Corrin, K. M.: Am. Pract. & Dig. Treatment 8:721 (May) 1957.

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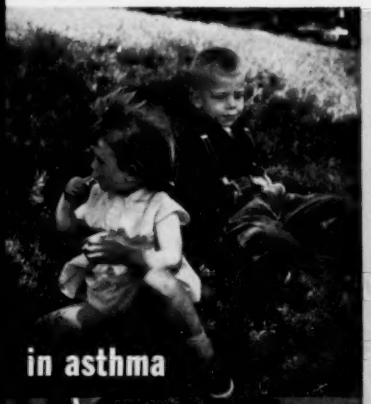
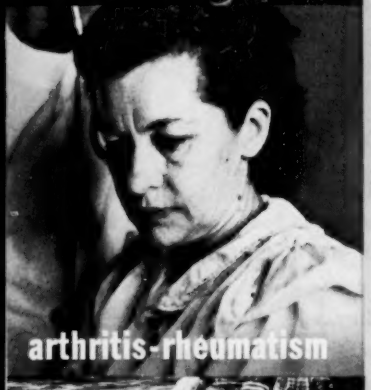
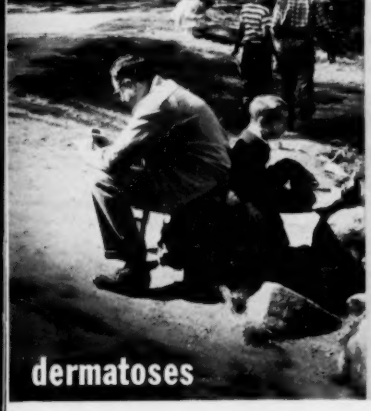


in asthma



arthritis-rheumatism



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1. Hutcheon, D. E., et al.: Paper presented at Am. Soc. Pharmacol. & Exper. Therap., Nov. 8-10, 1956, French Lick, Ind.
2. Johnston, T. G., and Cazort, A. G.: Clin. Rev. 1:17, 1958.
3. Warter, P. J.: J. M. Soc. New Jersey 54:7, 1957.
4. Individual Case Reports to Medical Dept., Pfizer Laboratories.
5. Strub, I. H.: To be published.

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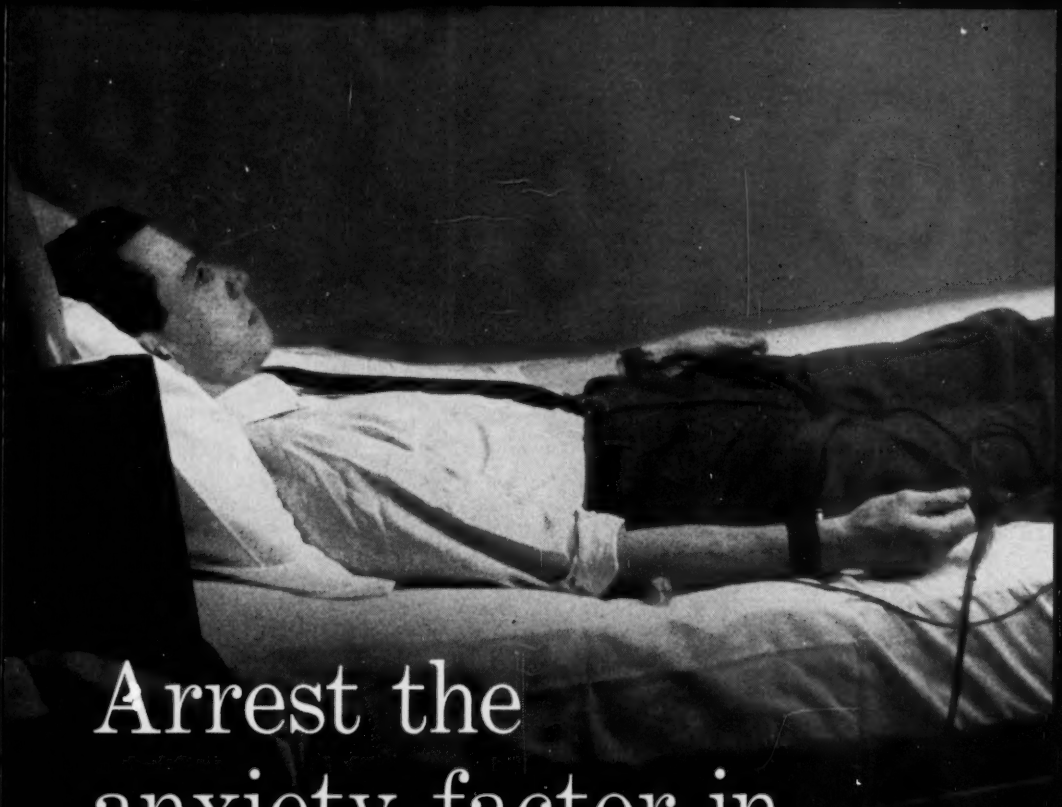

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*Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.

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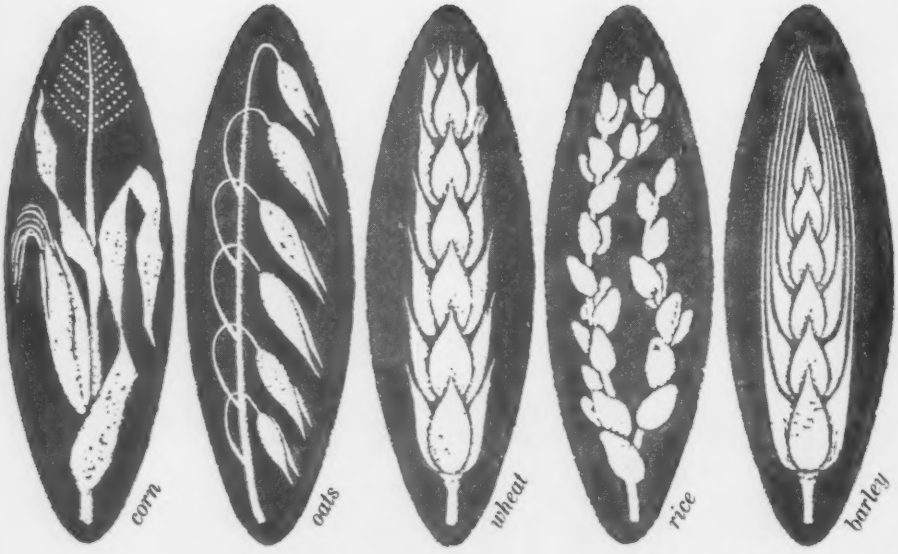

a moderate reduction in fat indicates cereal and milk serving

Medical and nutrition authorities recommend moderation and reasonableness in food choice as a best guide to good health. When a moderate reduction of dietary fat is indicated, a good choice is the cereal and milk serving for breakfast and the late evening snack.

Both the breakfast cereal and the milk contribute well-balanced nourishment and provide quick and lasting energy. This serving, as shown below, is a good source of many nutrients and provides about 10 per cent of the daily recommendations of high quality protein, important B vitamins, and essential minerals. Served with nonfat milk, the fat content is very low.*

nutritive composition of average cereal serving

	Cereal, 1 oz. Whole Milk, 4 oz. Sugar, 1 teaspoon	Cereal** 1 oz.	Whole Milk 4 oz.	Sugar 1 teaspoon
CALORIES	203	104	83	16
PROTEIN	7.3 gm.	3.1 gm.	4.2 gm.	
FAT	5.3 gm.	0.6 gm.	4.7 gm.*	
CARBOHYDRATE	32.2 gm.	22 gm.	6.0 gm.	4.2 gm.
CALCIUM	0.169 gm.	0.025 gm.	0.144 gm.	
IRON	1.5 mg.	1.4 mg.	0.1 mg.	
VITAMIN A	195 I. U.	—	195 I. U.	
THIAMINE	0.16 mg.	0.12 mg.	0.04 mg.	
RIBOFLAVIN	0.25 mg.	0.04 mg.	0.21 mg.	
NIACIN	1.4 mg.	1.3 mg.	0.1 mg.	
ASCORBIC ACID	1.5 mg.	—	1.5 mg.	
CHOLESTEROL	16.4 mg.	0	16.4 mg.*	

*Nonfat (skim) milk, 4 oz., reduces the Fat value to 0.1 gm. and the Cholesterol value to 0.35 mg.
**Based on composite average of breakfast cereals on dry weight basis.

Bowes, A. deP., and Church, C.F.: Food Values of Portions Commonly Used. 8th ed. Philadelphia: A. deP. Bowes. 1956.
Cereal Institute, Inc.: The Nutritional Contribution of Breakfast Cereals. Chicago: Cereal Institute, Inc., 1956.
Hayes, O. B., and Rose, G. K.: Supplementary Food Composition Table. J. Am. Dietet. A. 33:26, 1957.

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in dosage reduction

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in avoidance of new side effects

A minimal incidence of diabetogenic activity, edema, sodium or water retention, hypertension, or psychic reactions has been noted with DECADRON.[1,2,3,4] Other "classical" reactions were no more frequent or severe. DECADRON showed no increase in ulcerogenic potential, and **digestive complaints were rare. Nor have there been any new or "peculiar" side effects,** such as muscle wasting, leg cramps, weakness, depression, anorexia, weight loss, headache, dizziness, tachycardia, or erythema.

in therapeutic effectiveness

With DECADRON, investigators note "a decided intensification of the anti-inflammatory activity"[3] and antirheumatic potency.[4] Clinically, this was manifested by a **higher degree of improvement** in many patients previously treated with prednisteroids,[3] and by **achievement of satisfactory control in an impressive number of recalcitrant cases.**[3,4]

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More patients can be treated **more effectively** with DECADRON. Its higher anti-inflammatory potency frequently brings relief to cases resistant to other steroids. Relative freedom from diabetogenic effect in therapeutic dosage permits treatment of certain diabetics without an increase in insulin requirements. Minimal incidence of hypertension and of sodium and fluid retention allows effective therapy of many patients with cardiovascular disorders. And a healthy sense of well-being, reported by nearly all patients on DECADRON, assures excellent patient cooperation.

References:
1. Boland, E. W.: California Med. **88**:417 (June) 1958. 2. Bunim, J. J., et al.: Arthr. & Rheum. 1:313 (Aug.) 1958 3. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., June 21, 1958, San Francisco, Calif. 4. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., June 21, 1958, San Francisco, Calif.

To treat more patients more effectively in all allergic and inflammatory disorders amenable to corticosteroid therapy

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Usual dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime.
Dosage should be individualized.

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1. *Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card.* **1**:*395, March 1958.*
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* **8**:*504, Dec. 1957.*

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Characteristics: New Cortrophin-Zinc provides corticotropin of unsurpassed purity with low foreign protein content. This reduces the risk of sensitization reactions.

Since about 5% of the corticotropin is uncombined, onset of clinical response is rapid. But the balance, present as a complex of alpha zinc hydroxide, provides a prolonged action so that the effective time span of a single dose is usually several days. Injection of the new electrolytic Cortrophin-Zinc is virtually painless.

Pharmacology: A potent stimulator of cortical activity, Cortrophin-Zinc *does not depress* functioning of the suprarenal glands. Unlike the corticosteroids, adrenocorticotropic hormone arouses the adrenal glands to produce *natural* steroids in natural proportions. In a 5-year study of patients on ACTH therapy, no case of adrenal *or pituitary* depression or atrophy has been observed.

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Dosage should be individualized, but generally initial control of symptoms is obtained with a single injection of 40 Units of Cortrophin-Zinc daily until control is evident. Maintenance dosage is generally 20 Units (or less) twice a week.

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A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Of Scientific Thought

G. E. BURCH, M.D., New Orleans

Great scientific accomplishments require methodical, orderly, logical, and deliberate organization of thought and work. The planning of a good experiment is an experience limited to few men. A clear definition of objective, properly oriented within existing knowledge and previous publications, necessitates considerable effort, including self-conferences through scientific thought, with critical evaluation of any decision. Satisfactory and lucid planning requires leisurely but concentrated thought, even to the exclusion of one's entire environment or contact with reality.

Discipline in scientific thought is developed, self-taught, but nurtured by a good scientific environment, especially by minds of great scientists. Unfortunately, greatness is too often unrecognized by associates, for great people are simple, humble, modest people. To be *considered* great by some does not necessarily *confer* greatness. Too often, a man's prejudiced followers join to establish greatness in their "hero." Similarly, lack of contemporary recognition does not disqualify a great thinker. Time tells! It is the manipulation of important original ideas that glitters the mind of man. Display the data and ideas, and you reveal the level of scientific thought. Thought and research applied to a good, new idea are simple; interest and time influence success.

Pseudoscientists, on the other hand, are actors with artificially cultivated personalities. A great man need not act unnaturally or gather ideas of others and display them with pretense at originality; fortunately, he can never rationalize such action or escape his ever-present accusing conscience, the cardinal witness. Expropriation of another's idea and its display as original is scientifically dishonest, retards science, and deserves censure. This masquerade, known to oneself, never permits the true emotional satisfaction derived by the great scientist and discoverer. A scientific worker with second-hand ideas is a broker but is not, and can never be, a scientist and creator of ideas.

Discriminating is he who can distinguish a thinker from a masquerader. To mistake either may be disastrous. Since men with undesirable personal traits may sometimes produce great thoughts, personality should be ignored when ideas are the premium. Man may adopt artificial attitudes to dispel a lowly self-opinion, for great minds often are self-unrecognized. Usually, only great men can recognize and tolerate great thinkers whose personalities are not ordinary.

Abstract thinking provides mental gymnastics for anyone, even though he is primarily an experimenter. In thinking well, one conducts experiments abstractly. Thought quickly obviates useless experiments, eliminating unnecessary effort and

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From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana.

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expense, with only the thinker aware of the failures or errors encountered, unless he chooses to disclose them. Lucid thinking creates sharply defined, simple experiments, from which great discoveries usually germinate.

Abstract thinking provides all science with important tools, ideas, and concepts. The abstract thinker in theoretic physics enjoys the same respect in scientific fields as the abstract mathematician, whereas theoretic biology or medicine is practically nonexistent and generally unwelcome. This is particularly deficient in the clinical fields, including pathology, which is too often erroneously classified as a basic or nonclinical medical science, an error particularly evident today. Nevertheless, the biologic sciences are fertile for theoretic thought. Sharp definition of problems, evaluation of existing concepts, and better integration of reliable data to permit more valid conclusions, as well as creative thinking, are among the many fruitful theoretic phases of biology and medicine.

Rigid discipline in scientific thought must prevail at all times, even in clinical research, which can be as fundamental as nonclinical research, for the complexities of man, the most studied of all living things on earth, are not exceeded by those of any other animal. Furthermore, in biologic problems, remember, statistical and other mathematic symbolizations are often merely window dressing that provides a misleading favorable impression to nondiscriminating readers. An unscientific thought expressed in words does not become scientific by cloaking it in elaborate mathematic symbols. A good idea will stand the test of expression by any medium, i. e., word, picture, or diagram, and all ideas should be rigidly so tested.

Abstract thinking, ideally, should have the advantage of peace and solitude, although some can think well and actively in a "disturbing" environment. The ability to concentrate and withdraw into deep thought, oblivious of all, in an environment filled with intense stimuli is an enviable attribute. Silence in thought can provide rest and relaxation, even in a noisy environment, while one is creating ideas, integrating experiences, and evaluating thought. Such mental capacity is associated with great mental power; imagine the strength of the nation whose people possess such concentrative ability!

The great computor of man, enclosed in his calvaria, should seldom be turned off; it may operate at varying degrees of capacity and efficiency, in response to conscious commands. The ability to concentrate is reflected in the efficiency, magnitude, and quality of thought or computor performance. The efficiency with which the necessary variables are introduced and integrated into the thinking phenomenon, each with its proper coefficients, constitutes an index of the quality of scientific thought. Few men can concentrate continuously for prolonged periods; interruptions, usually external in origin, ultimately develop intracerebrally. Fortunate is he who can integrate the accomplishments of short intervals of thought interrupted by long intervals of time, packed with different and unrelated but important, interesting, and exciting experiences. The greater this capacity, the more productive the thinking.

The rambling mind merely scans the horizons. Scanning is fine, but a developed thought must not escape recognition. Thought, critical investigation, and analysis require extreme concentration. Exercise caution in a shift in thought, lest it be lost forever. Thinking brought to satisfactory conclusion brings satisfaction and comfort; incompleted thought, frustration. Rambling or flitting thought can yield no conclusion and cannot even be arrested long enough for testing. Lucid, effortless, methodic, deliberate thinking of a single problem, with purpose, remains most desirable and efficient. Thinking is the peculiar characteristic of man among all living things. He is without equal. The more and the greater the thought, the more man is man. Criteria of complete and adequate thoughtful investigation are without standard; time is the judge. All

evaluations and decisions must await the test of time. Thoughts may be evaluated quickly; others, posthumously; some, never.

There shall be thought as long as there is man; may its quality ever increase. Catalyze and protect thinking, the most cherished and powerful function of man. Creative minds should be patronized. Opportunity for thought, above all activities, must be made available by those charged with the responsibility of providing facilities for scientists. Clear mental channels for careful, efficient, successful integration of facts, concerned with important scientific problems. Delegate routine activities to average thinkers; free great minds. To feed the ultracomputor, the brain of man, with useless and senseless data burdens it unnecessarily and squanders computing time. Let each mind attain its own level of performance. Man himself knows the extent of the burden and of the freedom, he being the culprit in many instances in a loss of sense of values in self-indulgence and political maneuverings and aspirations.

Facts, data, and *knowledge* gathered through personal experience and, indirectly, through conversation and reading are the tools of thought; the brain, the machine; the environment, emotional drive, and state of health, sources of stimulation. But beware of entrance into foreign fields, regardless of how closely they may be related. Initially, the man out of his field is inadequate, awkward, and ineffective. To think properly, one must be thoroughly informed, armed with knowledge and ideas, essential raw materials for creative thought. The more precise the evaluation and integration of data, the more cogent the thought and the more reliable the conclusions. Of course, significant and proficient analytic thought requires valid data, evaluated objectively and without prejudice. It is the rare genius who accomplishes this without error. Just as it is imprudent to try to process reliable data through a poorly functioning, immature, inadequate mind, so is it unwise to feed faulty data into a good mind. No conclusions can be any more reliable than the data upon which they are founded. Useless is a great mind that handles unreliable data. But, like laboratory apparatus, fine mental equipment, properly operated, ensures excellent performance and product.

A healthy mind, richly charged with knowledge, imaginative, adventurous, and free to make associations, divorced from conventions and traditions, unharnessed by the past and unafraid of the present or future, will make contributions. Advancement is impossible for the traditionalist, who adheres to the accepted, lacks self-confidence, and is afraid of errors and the future. Unfortunately, acceptance of one's accomplishments usually requires conformance to the opinions of the traditionalist, who usually evaluates the performance.

The original or new idea is all. Original ideas are born of creative minds. Original creative thinking, easy for some, measures true advancement in science. The ordinary mind fired with another's original idea only *appears* to be great. The spark of a new idea explosively stimulates important research. Thought without a fine idea is associated with sluggish, useless, inefficient, and expensive pseudoinvestigation. Of course, careful, methodic, accurate, and active work, even though unplanned, may fortuitously result in an important discovery. This possibility, unlikely as it is, justifies support of many investigators and research programs. An able, alert, and active investigator, during a period of floundering, may generate a useful idea for subsequent, more effective investigation. The idea, deliberately and spontaneously generated or accidentally suggested by another's observation, is *all.* Idealess, unimaginative minds obstruct scientific advancement.

Too frequently, thoughts and ideas untestable by experiment are considered absurd and unrealistic. Nothing can be more erroneous. To consider thinking of value and importance only if it can immediately be tested experimentally is to limit thought to the current state of development of labora-

tory research. Let there be no restriction on constructive thought. Much healthy, creative thinking should be the aim of all men. Good thinking has value and purpose and benefits all mankind; selfish thoughts, not even oneself. Thinking good for others is good for oneself. No man with a thought can come to nought; a man without a thought is nought.

Contributions in logic made by mathematicians and theoretic physicists display the power of man's mind. Concepts, theories, hypotheses, and ideas of abstract thought remain to be tested in the laboratory, but the importance and future validation of good thought are certain, just as abstract thoughts have been in the past. A thought stimulates further thought, culminating ultimately in laboratory testing and verification. Proliferation of thought among men may exceed the original germinating abstract thought in importance.

Who is to judge, guide, or organize the thinking of man? Let good logical thinking be free, abundant, without restriction, and without imposition upon others. "Think as a sage and feel as a man." * Practical aims in abstract thinking are necessary only for immediate rewards. Hypothetic and theoretic concepts are foodstuff of scientists and their research. The significance of an idea is not related to the earliness or extent of its application, nor must the value of an idea be measured by its usefulness, material gains, or popular appeal. Great ideas are immortal products of the minds of mortal man. The immortality of any man is established by the immortality of his contributions.

Good science and thoughts never need defense or offense, both mirrors of weakness. Scientific thought and reason are for scientists, desired by many and available to few; but always exploit them. There are more unsolved problems in science than there are scientists. In scientific thought, remember, the present is yours; the experience of the past, material for thought in judgement of the future. Thoughts of today remain eternally under appraisal, for published thoughts remain forevermore, reflecting the nature of the parent mind.

For recognition of clinical research as a great biologic science, directly concerned with normal and abnormal man, scientific discipline in thought, with vision and unselfish dedication to science, must prevail. The belief that clinicians are never great thinkers in science is erroneous; the problems are biologic and ill and well man, the animal. As in any other field, little doctors have little minds, great doctors, great minds. Great responsibilities and problems of the clinician are his burden; to remain humble before them his virtue.

The idle mind is wasted and barren, the active mind, potentially productive. Think continuously; never leave the mind idle. To sit and think is not to loaf; loafers never think. He who thinks works; with thinking, reviewing, planning, and experimenting with lightening speed, events occur faster than can be related to others. So numerous are the details that some are never to be described. Judge not the thinker by his physical activity. The faker may hide behind a sham of thought, but time will reveal his accomplishments. To think and never to reveal one's findings accomplishes nothing for others, a selfish behavior. The mind of the thinker must tell; fear of embarrassment is the great inhibitor.

> The man who idly sits and thinks
> May sow a nobler crop than corn,
> For thoughts are seeds of future deeds,
> And when God thought the world was born! †

The minds of men of science are too often troubled. Rest the mind with diversional thought, to return to difficult problems with greater vigor. Conflicts and frustrations inhibit thought; rarely do great thoughts and deeds emanate from a burdened mind. Wholesome living without the burdens of self-created problems or faulty behavior fosters good thinking. Man who rarely thinks is dissatisfied; one engaged in scien-

* Modified from "The Hermit," by James Beattie.

† From "Inaction," by Harry Romain.

tific thought is not worried. An anxious, unhappy mind fatigues.

Properly motivated interest in science is conducive to scientific thought; solution of problems a pleasure. Keep problems important. The experiment is the test of a thought, a corollary of thinking. Healthy thinking is associated with well-planned, healthy research. Be not a fashionable researcher, with fluctuating interest, to avoid loneliness or to find support. Great accomplishments in thought follow independent thinking.

Thinking is a pleasant, quiet, peaceful hobby, supplied richly by the forces of the mind and its imagination. Leisurely thinking, without disturbance or interruption, can be an exciting and relaxing scientific experience. A strong mind may soothe a crippled body; a man unable to walk may sit and think. The fruits of his mind serve all, the service providing happiness even for the thinker. The habit of thinking is man's greatest; amateur thinkers can become professional. With scientific thought a hobby, thinking is play, not work. Thoughts of great problems are great games that all men can inexpensively play. Unlike material accomplishments, ideas and thought are available to rich and poor and are more likely to be produced by minds unhampered by wealth and its inevitable burdens.

The lucid, vivid thinker, supported by a retentive memory, "sees" and understands each phase of thought. Gaps in knowledge, understanding, and other phases of thought are evident to him. He may, consciously and for convenience and testing only, fill such gaps with assumptions, all thoroughly reconsidered and clearly labeled for himself and all to observe and to evaluate properly. Assumptions to him are conveniences in thought, never to be employed to deceive and always first indicated forcefully by him. Conclusions reached by continuity in logic, but linked by assumptions, can only be approximations, never final, and usually represent grossly erroneous decisions. The great thinker, forever aware and annoyed by gaps in thought and knowledge, is driven to his laboratory to investigate and concentrate on them, never satisfied until each is clarified.

He who uses assumptions as established facts is either dishonest, an amateur, or unable in scientific thought. Chains in logic, interrupted by gaps in knowledge, weaken at the point of the first assumption or gap and are forever in critical danger of serious difficulty and error. Scientific assumptions are like a pinhole in the hull of a ship; they make thought imperfect. Never be misled by assumptions, regardless of who makes them, and never accept as final a decision reached through them. Thought peppered with assumptions is merely trial thought. Assumptions, properly noted and evaluated, define unsolved problems. Assume no assumptions to be true. Truth needs no assumption. Definition and rule in thought, supported by assumptions, can serve useful scientific purposes, but decision and conclusions reached through them are limited by them. Assumptions are barriers. Absolute generalizations without limitations may not exist; if they did, they would be free of a single assumption.

Measure not a scientist by his tools, facts, but by his products, thoughts. The quality of a scientist is to be found in his thoughts, his deeds, a measure of them. Deeds reflect thought; tools may be deceptive. Memory, the mind's treasured warehouse of material and tools for thinking, is the power potential of thought. The memory depot should be neatly swept of trivia and minutiae, for great minds deal in great problems. Measure the mind by the quality of memory material. Little thoughts deal with little memories, great thoughts, with important memories. To pride oneself on recalling insignificant names and experiences from memory is to display a poor sense of value. Any able mind may so perform on command; small minds waste time and memory with such trivia. Display of such acts of memory is too often erroneously considered the expression of a great mind but actually reflects a misdirected mind.

People whose memory functions are cluttered with trivia, many erroneous, are never

great. Too often, the sole objective of mental effort is directed at developing and expanding memory and "filling" it with unselected, unestablished facts to become a "walking library" or encyclopedia, always in search of an opportunity to display "remarkable" memory functions. Such minds inevitably provide unreliability and distortion of the original, never think creatively or with originality but only present in different fashion that which is already available and known. Without creative thinking, such minds never cause progress directly but merely serve, at times, as a convenience for others, especially lazy creative thinkers. They may be an interesting curiosity but are usually "cowards" in scientific thought. A mind infused with obsessions, confusions, frustrations, and feelings of inferiority often compensates by "showing off" with the thoughts of others.

To question, wonder about, doubt all about, and observe events brings thought and study. Take nothing for granted; accept all as transitory. The fundamental events of nature, once understood, are simple. An idea or concept, when considered simple and obvious to others, has reached an ultimate in crystallization.

Those who produce the idea, outline the objectives, and organize the experiments by careful and meticulous thinking make the fundamental contribution. Creative thinking by a peaceful mind and absorbing interest cannot be bought; technologic thinking can. Others of ability who test, develop, and engineer the program, and make fewer fundamental contributions, require technologic training and thought. Practically all clinicians are in this category; whether this be fortunate or unfortunate remains unknown.

Thought can never be too intense, too profound, or too fundamental in approach to a problem. May science never be satisfied, its standards never too high, the qualifications of the minds of its men and efforts never limited. The greater the scientific approach of any phase of science, the greater its growth. Nations and empires perish when they become complacent about their scientific state; progress ceases, and decay sets in, to be superseded by nations scientifically alert.

Unfortunately, the mind of man is rarely programed for creative and generative thought; preoccupied it is with overcoming passive and active resistance offered by the skeptic, traditionalist, phlegmatic, satisfied, greedy, selfish, and self-indulgent. Unfortunately, merely routine living leaves little time for creative thought, for training, teaching, doing, telling. With so little time for free thinking from birth to death, no wonder man rarely thinks creatively. He still struggles to survive, even though society and law protect the unfit with equal attention and rights as the fittest.

The time will come when man will really think; this will be a pleasure, in fact, a routine for all. Ultra-automation will accomplish the everyday jobs. Recognition by material wealth and political power will not be desired; rather, thinking will be the ultimate goal. Why be satisfied with the mind of today, used so little and so timidly? Why be embarrassed by mental accomplishments, the envy and subject of idle gossip of associates, do-nothings, and materialistic and power politicians who prefer attack to praise? But "A prophet is not without honour save in his own country. . . ."‡ Yet thought and work ultimately bring great benefits to all.

The greatest natural resource of any nation are the minds of its people. From the air, ocean, and land, the mind of man develops all the needs of man. Think hard, think much, observe, discover, and tell; convert the energy of a handful of foodstuffs to power and wealth for all. The health of man, the workings of man, the surroundings of man are all to be improved, described, and told through the effort of his mind.

‡ Matthew XIV:46.

The Mind of Man

The mind of man, all of science
To achieve and to desire.
The thoughts of man by mind of man
Discovers all that we require.
The mind of man, keep it on
To fetch ideas from the sky.
Never limit the mind of man;
Let it forever be on the fly.
The mind of man, the peace of man
To comfort man whene'er he writhe.
Develop it men, with all thy might,
For it hath no limit to diversify.
The mind of man, the sorrow of man
In response not to provide.
Total use and total care
Turn it on, keep it on or else we cry.
The mind of man, the power of man
Without we'd succumb e'en to the fly.
Use it men for forever more
'Tis it we use or else we die.

Tulane University School of Medicine, Department of Medicine, 1430 Tulane Ave. (12).

Practical Clinical Physiology of Pulmonary Disease

Causes and Differential Diagnosis of Cyanosis of Cardiopulmonary Origin

JULIUS H. COMROE Jr., M.D., San Francisco

The major function of the lungs is to arterialize the venous blood. This requires the addition of sufficient oxygen to maintain normal saturation of hemoglobin in the arterial blood (about 97%-98%) and the removal of enough carbon dioxide to maintain the arterial CO_2 tension at about 40 mm. Hg and the arterial pH between 7.39 and 7.41.

The lung provides a magnificent mechanism for the exchange of gases between pulmonary capillary blood and air. The surface area of the pulmonary alveoli is estimated to be as high as 90 square meters, and gas in the air sacs is separated only by alveolar-capillary membranes as thin as 0.1μ from venous blood in a capillary bed estimated to have a surface area as high as 50 square meters.

There are only a few requirements for adequate pulmonary oxygen exchange [1]:

1. A volume of air must be drawn past the conducting airway (anatomical dead space) into the alveoli sufficient to supply the O_2 requirements of the body regardless of the level of O_2 consumption.

2. This air must be either distributed evenly to the millions of alveoli (if capillary blood flow is also uniform) or supplied to each alveolus in proportion to the volume of blood flowing through the capillaries surrounding each alveolus (in the event that pulmonary capillary blood flow is not uniform).

3. There should be no unusual barrier to the diffusion of O_2 across the alveolar-capillary membranes.

4. The blood flowing through the pulmonary capillary bed should be in intimate contact with ventilated alveoli and, as indicated above, should be distributed either uniformly or in proportion to the ventilation of each alveolus.

5. The volume of pulmonary blood flow per minute must be sufficient to carry the amount of O_2 required by the tissues each minute.

Arterial anoxemia of cardiopulmonary origin can occur only because of: (*a*) inadequate volume of alveolar ventilation, (*b*) uneven alveolar ventilation in relation to pulmonary capillary blood flow, (*c*) impairment of alveolar capillary diffusion, (*d*) the shunting of mixed venous blood around ventilated alveoli, or (*e*) combinations of these types.

Arterial anoxemia can occur in other conditions if the patient breathes air at low total pressure (high altitude), inhales carbon monoxide, or has had some active hemoglobin converted into inactive forms (such as *met* hemoglobin). However, these are not of cardiopulmonary origin and will not be discussed here. Cyanosis (*without arterial*

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anoxemia) can occur because of local or general reduction in blood flow to a part, resulting in the extraction of greater than normal amounts of O_2 from each unit of blood in order to supply the oxygen needs of the tissues. Since this is not *arterial* anoxemia, it will not be discussed here.

Causes of Arterial Anoxemia of Cardiopulmonary Origin

(*a*) *Inadequate Volume of Alveolar Ventilation.*—Several matters deserve emphasis here:

1. Rate of breathing alone and depth of breathing alone give no true information about the adequacy of alveolar ventilation. Rate × depth = minute volume, and this is a better guide. This may be measured by using a simple spirometer or by a bag and gas meter.

2. Only that volume of inspired air which reaches the business end of the lungs, the alveoli, is *useful* ventilation. Therefore, the volume of *useful*, or alveolar, ventilation is far more important than the volume of minute ventilation. Useful, or alveolar, ventilation per minute = rate × (depth − anatomical dead-space volume). Anatomical dead space in milliliters in adults is approximately equal to the predicted normal weight of the patient in pounds.[2] Thus, the alveolar ventilation of a 150 lb. man breathing 450 ml. of air 20 times per minute is approximately $20 \times (450 - 150) = 6000$ ml. per minute.

3. There is no normal value for minute or alveolar ventilation; it must be related to the metabolic activity of each person, which is usually measured by his oxygen requirements or CO_2 production. Therefore, the adequacy of alveolar ventilation should be judged best by the level of O_2 and CO_2 in the arterial blood. Since (*b*), (*c*), and (*d*) (see above) may alter arterial O_2 significantly but do not change arterial CO_2 levels drastically, abnormally high arterial pCO_2 rather than abnormally low arterial O_2 is usually used to judge hypoventilation. Obviously, if a 150 lb. adult at rest is ventilating only 2-4 instead of 6-8 liters per minute, he is hypoventilating; when there is doubt, the level of arterial pCO_2 provides accurate information.

4. Hypoventilation can be caused by many factors; the "hypoventilation syndrome" may be due to depression of the respiratory center in the medulla, damage to the nervous pathways between the medulla and the respiratory muscles, disease of the peripheral neuromuscular apparatus, fixation of the thorax, decreased compliance of the lungs, or obstruction of the airways. Differential diagnosis can be achieved in part by noting the response to inhaled 7.5% to 10% CO_2 and by the use of an esophageal balloon to estimate intrathoracic pressure changes with inspiration. If there is insufficient force acting on the thorax or if there is thoracic fixation, pressure fluctuations and ventilation will be minimal with maximal effort; if there is pulmonary rigidity or airway obstruction, pressure fluctuations will be great but ventilation will be insufficient despite maximal effort.

(*b*) *Uneven Alveolar Ventilation in Relation to Pulmonary Capillary Blood Flow.*—Normally a healthy man at rest requires about 4 liters of alveolar ventilation to oxygenate 5 liters of blood flowing through the pulmonary capillaries. If there is a ratio of 4:5 in every region of the lungs, the blood will be properly oxygenated; if it is higher in some areas and lower in others, arterial anoxemia must result. This is because increased ventilation cannot superoxygenate blood (blood is almost maximally oxygenated at normal levels of alveolar ventilation), but decreased ventilation must result in decreased amounts of O_2 in the arterial blood. Since hyperventilated areas cannot correct for hypoventilated areas so far as arterial O_2 is concerned, uneven alveolar ventilation in relation to pulmonary capillary blood flow must result in anoxemia. *This is the commonest cause of arterial anoxemia seen by the physician.* It includes uneven ventilation due to regional obstruction (asthma, emphysema, bronchitis, organic obstruction) or to regional changes in pulmonary compli-

ance (fibrosis, compression, infection, congestion, edema, effusion). It includes uneven circulation due to obstruction by emboli, vascular sclerosis, or obliteration. If there is no absolute shunting of mixed venous blood past ventilated alveoli, anoxemia caused by uneven distribution can always be corrected by the inhalation of oxygen (though this will not correct any accumulation of CO_2 that may result from over-all alveolar hypoventilation); anoxemia caused by hypoventilation alone (see [*a*] above) can always be corrected by *adequate ventilation with air* without the necessity of using O_2.

(*c*) *Impairment of Alveolar Capillary Diffusion.*—From the practical point of view, impairment of diffusion affects only the oxygenating mechanism of the lung and not that for CO_2 removal, because of the lesser solubility and diffusibility of O_2. The diffusion of O_2 is influenced by the length of the path it must traverse to cross the alveolar-capillary membranes and by the surface area of ventilated alveoli in contact with functioning pulmonary capillaries. The *length* of the path is increased (alveolar-capillary block) when the alveolar membrane is thicker; when there is separation of the alveolar and capillary membranes by edema fluid, exudate, or fibrous tissue, or when the capillary membrane is thickened. The functioning surface *area* is decreased by many diseases of alveoli, septa, or capillaries. The patient who has definite impairment of diffusion may have no arterial anoxemia while resting but usually develops it during exercise. However, this alone is not sufficient for a specific diagnosis because most types of arterial anoxemia become severer during exercise. Again, the anoxemia caused by impaired diffusion is corrected by inhalation of O_2 but, likewise, this is not a specific test. Clinically, impairment of diffusion is suspected in patients with clinical and radiological evidence compatible with the diagnosis, who have anoxemia associated with alveolar *hyper*ventilation and normal or decreased values for arterial CO_2 pressure, a decreased vital capacity but no parallel reduction in maximum breathing capacity.

The surest method of diagnosing impairment of diffusion during life, without biopsy (and possibly early in the course of the disease) is the use of one of the carbon monoxide tests of diffusing capacity of the lung.[3,4] By studying the rate of uptake of CO during the inhalation of low, nontoxic concentrations of this gas for short periods of time (10 seconds to several minutes), one can learn whether diffusion is normal or impaired; one cannot learn however whether impairment is due to alveolar-capillary block (longer path) or to reduction in functioning surface area of alveolar-capillary membranes.

(*d*) *The Shunting of Mixed Venous Blood Around Ventilated Alveoli.*—This must cause anoxemia in a subject breathing air, because some mixed venous poorly oxygenated blood bypasses the air sacs and cannot become better oxygenated. Since inhalation of oxygen cannot, under these circumstances, bring arterial blood O_2 to maximal values but does fully oxygenate the blood of patients with hypoventilation, uneven distribution, or impaired diffusion, an oxygen test serves to identify the existence of venous-to-arterial shunts. The pulmonary physiologist gives the patient 100% O_2 to breathe for 15-20 minutes and then removes a sample of arterial blood. If it contains fully saturated hemoglobin *plus* 2.0 cc. of dissolved O_2 per 100 cc. of blood, no shunt existed at the time of the test. Since the high pressure of O_2 in the alveoli and in the blood (673 mm. Hg) when the patient breathes O_2 causes much more O_2 to dissolve physically in the blood (2.0 cc/100 cc.) than when the patient breathes air (alveolar pO_2 100 mm. Hg; dissolved O_2 0.3 cc/100 cc.), a venous-arterial shunt cannot be excluded unless both hemoglobin and plasma contain the maximal amount of O_2. The O_2 test merely proves the presence of a shunt but does not identify its type or location;

it may be intrapulmonary (hemangioma, pulmonary atelectasis) or intracardiac (congenital or acquired defect).

(*e*) *Mixed Types.*—Occasionally pulmonary disease occurs in pure form; more often abnormalities in distribution, diffusion, and even in ventilation occur together to form a more complicated pattern.

Plan for Diagnosis of Arterial Anoxemia of Cardiopulmonary Origin

First, measure minute ventilation and calculate alveolar ventilation. If there is no significant hypoventilation, then perform the O_2 test. If arterial blood O_2 values rise to a maximum, there is no venous-arterial shunt and the diagnosis must be either uneven distribution or impaired diffusion or both. Clinical judgment, radiological studies, and further pulmonary function tests (CO-diffusing capacity, single-breath N_2 meter test,[5] and studies of the mechanical properties of the lungs[1]) can then identify precisely the cause of the anoxemia and suggest proper therapy.

University of California Medical Center, Cardiovascular Research Institute.

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Physiologic Considerations in the Diagnosis and Treatment of Ventilatory Insufficiency

WARD S. FOWLER, M.D., and R. DREW MILLER, M.D., Rochester, Minn.

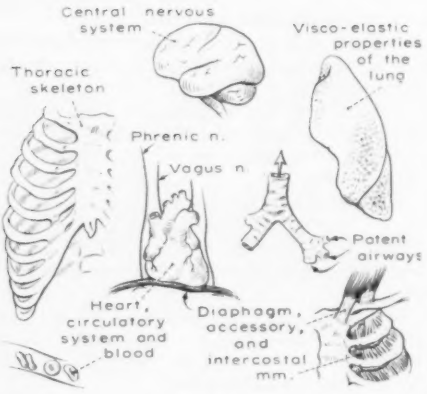

Fig. 1.—Some of the structures whose integrated activity is required for efficient and easy breathing.

"Ventilatory insufficiency" is a brief expression used to indicate a complex situation that exists when an abnormality in the mechanical aspects of breathing is accompanied by dyspnea at moderate levels of physical activity.

The numerous structures contributing to breathing (Fig. 1) emphasize the complexity of the actual mechanics of breathing. Fenn [1] has aptly stated, ". . . the mechanics of breathing is a problem requiring on one hand the detailed knowledge of a classical anatomist and on the other hand the analytic understanding of an engineer." It may be permissible to add that much remains to be accomplished in the synthesis of understanding of (1) how the integrated activity of the breathing structures is maintained in health or lost to varying degrees in disease and (2) the basis and mechanism of dyspnea.

In recent years, however, the application of methods and principles of respiratory physiology has provided several measures of established utility in the diagnosis and management of ventilatory disorders.

Mechanical Devices Useful in Maintaining Ventilation

Effective mechanical devices have been developed for assisting or maintaining ventilation by controlled application of air pressure to the upper airway. Largely by virtue of mechanical flexibility and small size, these represent useful additions to the older types of ventilators, such as the cuirass and body respirators. Devices are available for administering selected gases under intermittent positive pressure, with selection of the level and duration of pressure under control of either the patient or the operator. These also provide convenient and effective means of administering nebulized medicaments, although this can be accomplished satisfactorily and more economically in many cases with simpler nebulizers alone. Pressure-breathing devices might be used more efficiently if they provided an indicator of the tidal volume actually achieved. Also available are portable devices that in medical jargon are called "cough machines" and that provide exsufflation with negative pressure (EWNP). These are designed to augment or provide the forceful cough needed for

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prevention or relief of retention of bronchial secretions. Use of any of these pressure-breathing devices can be harmful if they are applied improperly.

Apparatus for generating mist or fog has proved effective in providing sufficient water in inspired gases to prevent evaporation from the airway mucosa.

Ventilatory Tests

Another measure of established value is the use of ventilatory tests which provide objective measurements of the performance of the respiratory bellows. These include measurement of the conventional vital capacity, the rapid or timed vital capacity, and the maximal breathing capacity. In our experience these are the most widely useful of currently available tests of pulmonary function. All may be done quickly with reasonably simple and reliable apparatus, a variety of which are commercially available. A principal advantage of using a recording spirometer is that the physician with some experience can quickly evaluate by inspection whether the tests have been performed satisfactorily if they are conducted by laboratory assistants. These tests provide a measure of the type and extent of ventilatory dysfunction. The anatomic or pathologic basis for an abnormal test usually must be defined by, or in conjunction with, other methods of diagnosis, and proper interpretation of the results of the tests necessitates their integration with the other aspects of the particular clinical problem.

Uses of the Ventilatory Tests

Perhaps the most frequent use of ventilatory tests is for quantitative assessment of ventilatory capacity in patients with chronic bronchitis or emphysema or both. To a smaller extent they are useful in confirming or excluding a clinical diagnosis of diffuse obstructive emphysema. The limited accuracy of diagnosis of emphysema by clinical examination has been noted by Christie,[2] and Fletcher [3] has concluded, ". . . there is little hope of the clinician's being able to diagnose the early stages." In some patients only minimal or equivocal abnormalities may be found by physical examination, but their ventilatory tests may clearly show the presence of an obstructive type of ventilatory abnormality. This may be illustrated by the case of a 59-year-old man whose chief complaint was increasing exertional dyspnea of four years' duration. Significant physical findings were limited to slight decrease in breath sounds and some expiratory slowing during rapid deep breathing. The results of spirographic tests (Fig. 2) showed marked expiratory retardation, although a relatively large volume could be expired if sufficient time was taken. Measurements of

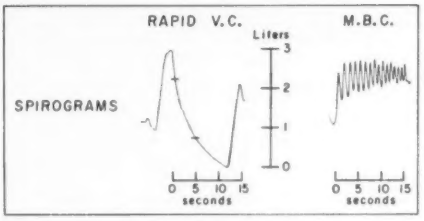
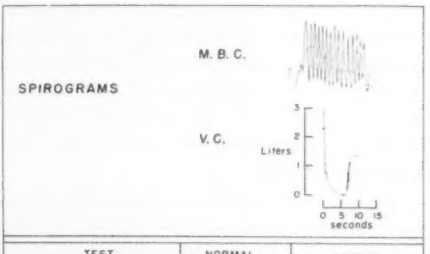


Fig. 2.—Results of ventilatory tests in a patient with emphysema. In the spirogram, expiration is downward. The values and their percentage of the predicted normal were as follows: Vital capacity (V. C.), 3.0 liters (75%). Maximal breathing capacity (M. B. C.), 42 liters per minute (47%). Maximal midexpiratory flow, 0.4 liter per second (11%).



TEST	NORMAL	
Vital Capacity (L.)	4.9	3.1
Max. Breathing Capacity (L./minute)	116	100
Max. Midexpiratory Flow (L./second)	> 2.0	2.5
Total Capacity (L.)	6.6	3.9
7 minute N_2 Index (%)	< 2.5	0.3
Arterial O_2 Saturation (%)	95–98	
Rest		98
Exercise		90

Fig. 3.—Results of tests of pulmonary function on patient with diffuse pulmonary fibrosis. (M. B. C. indicates maximal breathing capacity; V. C., vital capacity.)

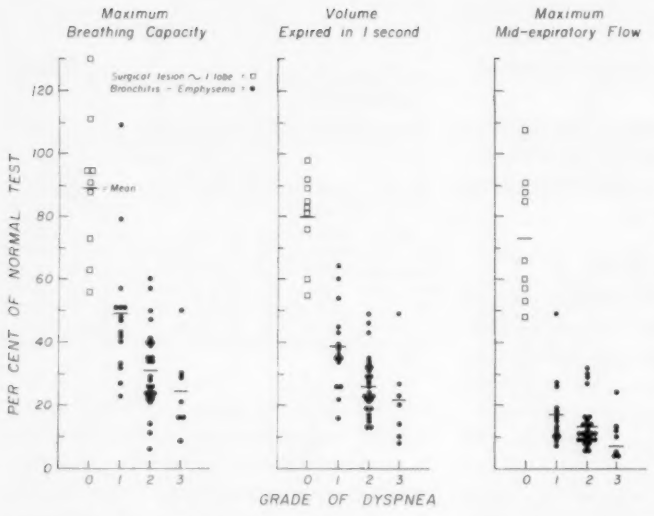


Fig. 4.—Relation between degree of dyspnea and abnormality of several ventilatory tests in patients with chronic bronchitis or emphysema or both. Normal values for maximal breathing capacity and vital capacity were predicted from formulas of Baldwin and associates[4] and maximal midexpiratory flow from Leuallen and Fowler.[6] Values for volume expired in one second are the ratio of the volume actually expired in one second to the predicted total vital capacity; this normally exceeds 65% to 70%.

the rate of flow, either on the rapid vital capacity or by the maximal breathing capacity, showed impairments that would not be appreciated by measuring only the volume of the vital capacity. Other tests also established the presence of an increased residual volume (the volume of gas in the lungs after maximal exhalation) and of retarded alveolar ventilation of considerable regions of the lungs, shown by abnormally large concentrations of nitrogen remaining after inhalation of oxygen for seven minutes. Measurement of the residual volume has been widely advocated as necessary for accurate diagnosis and quantitation of emphysema, but unfortunately the required methods are still too complex to be used economically except in institutions of considerable size or special interest.

The type of ventilatory insufficiency associated with reduced distensibility of the lungs or thoracic cage but without notably increased resistance to the flow of air is usually called "restrictive." This may be illustrated by the results of tests (Fig. 3) on a 63-year-old man whose chief complaints were fatigue, exertional dyspnea, and early morning coughing of one year's duration. Many fine rales were heard over the lower half of both lungs. Roentgenograms of the thorax showed evidence of thickened basal pleurae and diffuse bilateral pulmonary fibrosis, the etiology of which was not established. Spirographic recordings of the vital capacity alone indicated a ventilatory abnormality consistent with reduced distensibility of the lungs without the obstructive characteristic of retarded flow. The decrease in arterial oxygen saturation with exercise is attributable in this case to a decreased diffusing capacity, as in the syndrome of alveolocapillary block.

The difficulties in clinical diagnosis of the early stages of diffuse obstructive emphysema have been noted previously. We believe that more extensive use of the relatively simple ventilatory tests could be helpful. This view is based in part on the observations illustrated in Figure 4. In that Figure the results of ventilatory tests on 50 consecutive patients with chronic, usually asthmatic, bronchitis or emphysema or both were related to the extent of dyspnea as noted on their case records.* Grades 1, 2, and 3 of dyspnea correspond respectively with Classes

* The diagnosis in each case was made on the basis of the history, physical and roentgenologic examination, and results of pulmonary function tests. The brief summary of the history and examination of the two patients illustrated by Figures 2 and 3 is not intended to represent a complete report.

II, III, and IV of the New York Heart Association's classification of function. Patients having dyspnea of Grade 1 had slight to moderate limitation of activity as a result of dyspnea. They could walk more than a block on the level at a normal pace or climb one flight of stairs without stopping. Patients with dyspnea of Grade 2 could not walk one block at a normal pace without stopping to rest. Those with dyspnea of Grade 3 were dyspneic at rest and usually were forced to rest after walking a few steps. To illustrate the results in patients without dyspnea, we have used a small group of patients who had various pulmonary lesions, later removed surgically, that were limited to the extent of about one lobe.

The relationship between the reduction of maximal breathing capacity and the extent of dyspnea is similar to that found in numerous previous studies and has led some authors to state that reduced maximal breathing capacity reflecting limited ventilatory reserve is the cause of dyspnea. In contrast, we should like to emphasize the weakness of the correlation. None of the several tests discriminates well between patients with dyspnea Grade 1, who were usually capable of working and the nearly bedridden patients with Grade 3 dyspnea. Equally poor correlations were obtained by Gilson and Hugh-Jones,[6] even though they used a method for grading dyspnea that was shown experimentally to be reproducible. This emphasizes how far the physiologist has yet to go in developing both understanding and clinically practical methods of measurement of the factors responsible for dyspnea, as clearly pointed out by Comroe.[7]

To return to the problem of early diagnosis, attention is drawn to the fact that the maximal midexpiratory flow (the rate of flow of the middle half of a maximally rapid and deep exhalation) is reduced to about 20% of normal in patients with dyspnea Grade 1. One wonders whether this means that the irreversible aspects of the disease have become of major extent before symptoms have become sufficient to cause the patients to seek medical attention. If so, it is apparent that relatively simple methods of examination are available for detecting less serious abnormalities, the prompt treatment of which might reverse or retard the development of more advanced emphysema.

The symptomatic improvement often provided by bronchodilating drugs for patients with bronchitis and emphysema is well known. Ventilatory tests may be used after administration of bronchodilators to obtain objective measurements of improvement. The results of several tests after administration of a bronchodilating aerosol to the same 50 patients as in Figure 4 are shown

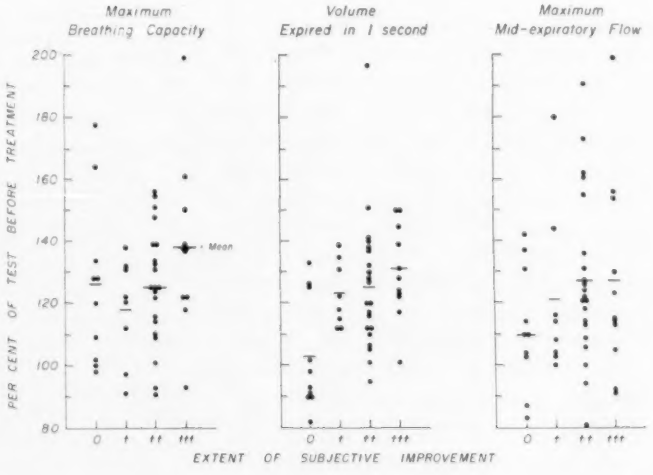


Fig. 5.—Relation between degree of subjective and objective improvement after administration of an oxygen-generated bronchodilating aerosol (isoproterenol solution) to patients with chronic bronchitis or emphysema or both.

in Figure 5. The extent of subjective improvement of dyspnea and the ease of breathing were judged by the patients' statements, obtained about 4 to 24 hours after use of the bronchodilator. The three grades of improvement may be roughly characterized as some, moderate, and much. Both subjective and objective improvement of some extent occurred in the large majority of patients. However, the striking feature is the poor correlation. This again emphasizes the current limitations of practical measurement of factors related to dyspnea.

This lack of correlation between subjective and objective results indicates the importance of obtaining both types of information. The absence of objective improvement in the tests illustrated is by itself insufficient evidence to conclude that bronchodilating drugs will not benefit the patient. The clinician might be more inclined to undertake an extended therapeutic trial if one or both of the results show some promise of benefit.

Comment

We have mentioned only a few of the physiologic aspects of ventilatory insufficiency. It seems clear that the development of practical and objective ventilatory tests, pressure breathing devices, and mist generators provides real and useful recent additions to the variety of procedures available for diagnosis and management of ventilatory problems.

Mayo Clinic.

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The Clinical Application of the Artificial Kidney

An Evaluation of the Management of Acute Renal Failure with Dialysis

W. A. KELEMEN, M.D., and W. J. KOLFF, M.D., Cleveland

This paper proposes to analyze data obtained on 38 patients with acute renal failure treated by dialysis at the Cleveland Clinic Hospital in 1957 and to demonstrate the use of a punch-card system for correlating 166 variables. The latter deserves wider use, and if generally adopted for analysis of acute renal failure, a nation-wide survey might profitably be done.*

Methods

Fluid intake was restricted to 600 ml/24 hours if anuria existed.[1] Electrolytes were not administered unless they were demonstrably lost.[2] A forced high-caloric low-protein regimen was instituted as far as was practical.[3] If dialysis was indicated, twin-coil artificial kidneys† were used. The technique has been described.[4-6]

The purpose of the artificial kidney is to remove retention products and correct electrolyte abnormalities; at the same time ultrafiltration may remove edema fluid. In small children only one coil was utilized and dialysis was done for four hours.[7] In adults dialysis lasted six hours. The radial arteries or greater saphenous veins were used to draw blood from the patient; any other vein, to return it. Usually polyvinylchloride catheters were used. They were previously heated in hot liquid petrolatum (mineral oil), drawn out in taper, and cut in appropriate sizes. For the saphenous vein plastic tubing of sizes 12, 14 or 16 F. with multiple holes was utilized. It was inserted to the level of the inferior vena cava. The catheter was left in place for continuous administration of 40% invert sugar (Travert†) if needed. Bacitracin ointment was used to cover the greater saphenous cut-down site. If hemorrhage was anticipated, regional heparinization was used to reduce or eliminate any systemic heparin effect. While heparin was being administered by constant drip under pressure to the blood inflow tube to the artificial kidney, protamine sulfate was simultaneously administered to the outflow tube.[8]

Analysis of Data

In order to organize our data a McBee § punch card with 166 holes was devised as shown by Figure 1. Each question is made specific and answerable by either yes or no. Moreover, sufficient space is provided at the side of each question so that numerical data can be filled in. The positive answers are punched out. When an ice pick is placed through a hole in a stack of these cards, the cards with the positive answers fall out. The two groups of cards thus selected represent certain categories and can be counted. Each group can be ice-picked again for any of the 165 remaining questions, etc. Comparisons and analyses can be made in a matter of minutes. Moreover, short summaries are immediately available on the cards.

Certain numbers are found by elimination; for example, take the stack of cards

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* We are able to provide others with a sufficient number of these cards to determine their usefulness.

† Travenol, subsidiary of Baxter Laboratories, Morton Grove, Ill.

§ Royal McBee Corporation, Port Chester, N. Y.

Figure 1

of patients who died and remove the cards representing irrecoverable disease, and the remaining cards represent potentially recoverable patients unsuccessfully treated. One card can summarize a whole stack; thus, all the data concerning 38 patients in acute renal failure are summarized on the one card shown in Figure 2.

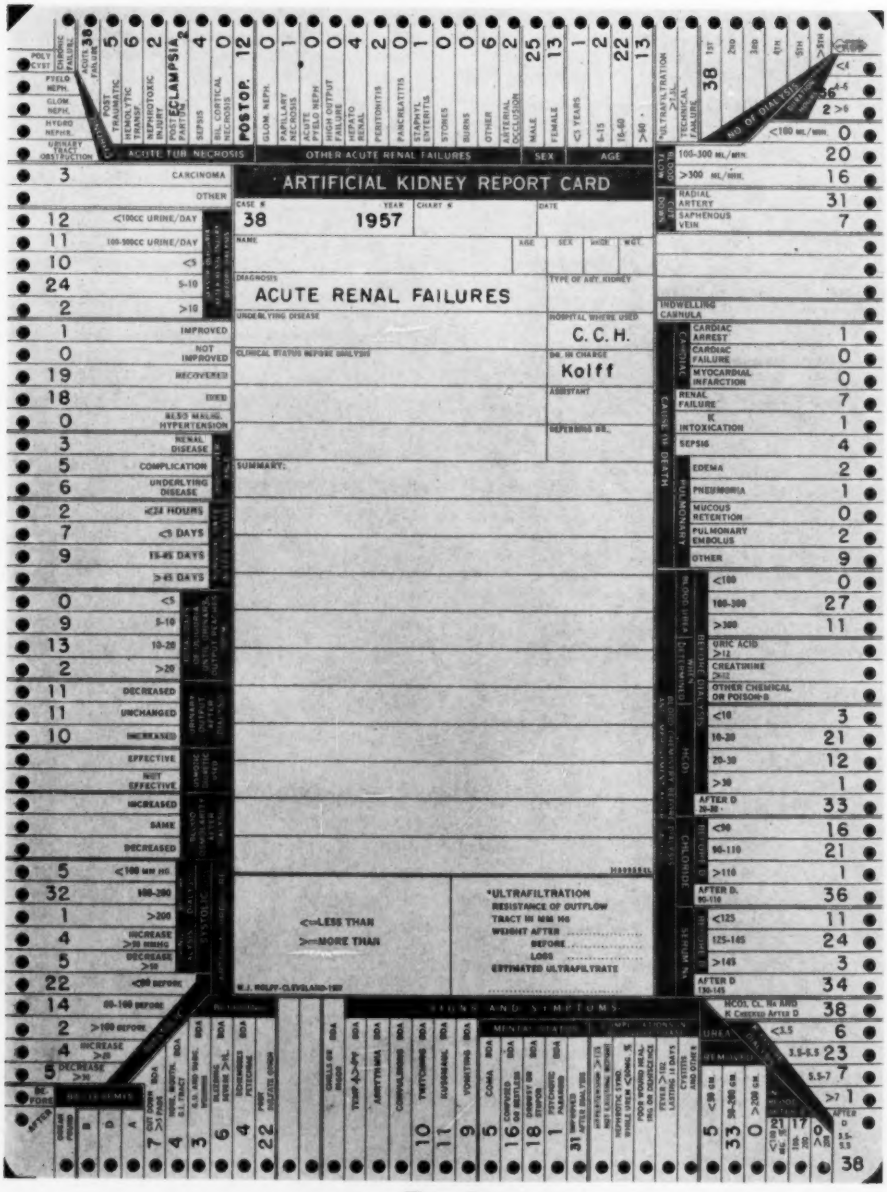

Figure 2

Results and Comment

The over-all recovery rate was 52%; the recovery rate of females (7 of 13) was not significantly higher than of males (12 of 25). Acute renal failure is no reason to give up hope in old people. Of the 13 patients older than sixty, 5 recovered, and, of the 8 who died, 7 had what is considered as irrecoverable disease and 1 died of unknown causes. In the 38 patients the artificial

TABLE 1.—*Diagnoses and Causes of Acute Renal Failure in Thirty-Eight Patients with Acute Renal Failure and Survival Rate* *

Diagnoses	Patients, No.	Survivals	Deaths
Post-traumatic	5	3	2
Postoperative	12	4	8
Hemolytic transfusion	6	4	2
Nephrotoxic injury	2	2	0
Postpartum	0	0	0
Eclampsia	2	2	0
Sepsis	4	3	1
Bilateral cortical necrosis	0	0	0
Acute glomerulonephritis	0	0	0
Papillary necrosis	1	0	1
Acute pyelonephritis	0	0	0
Hepatorenal syndrome	4	1	3
Peritonitis	2	0	2
Pancreatitis	0	0	0
Staph. enteritis	1	1	0
Stones	0	0	0
Burns	0	0	0
Arterial occlusion	2	0	2
High output failure	0	0	0
Other †	6	2	4

* Table 1 corresponds to the upper part of the punch card (Fig. 1) and lists the usual forms of acute tubular necrosis first. As some patients had more than one cause for acute renal shutdown, some duplication has occurred.

† N_2 asphyxiation; Henoch-Schönlein purpura (two); carcinoma (three), of which two were obstructing the ureters.

TABLE 2.—*Differentiation of Fourteen Cases of Irrecoverable Disease* *

	Total
Renal disease †	3
Complication ‡	5
Underlying disease §	6

* This Table corresponds to the middle of the left side of the punch card (Fig. 1).

† 2 Occlusions of renal arteries; 1 Necrotizing papillitis.

‡ 3 Complicated aortic and femoral grafts; 1 Generalized peritonitis; 1 Pulmonary fat embolus.

§ 1 Henoch-Schönlein purpura with acute nephritis; 1 Necrotizing anglitis; 2 Carcinomas, pancreas and retroperitoneum; 1 Hepatocellular necrosis with hepatic duct stones; 1 Biliary cirrhosis with ammonia intoxication.

kidney was used 69 times. Four patients needed four dialyses each: three lived and one died.

Diagnoses and Causes of Acute Renal Failure.—Table 1 corresponds to the upper part of the punch card and lists the usual forms of acute tubular necrosis first. Other causes of acute renal failure follow. Of the six patients with hemolytic transfusion reactions, four recovered. Of the five patients with post-traumatic oliguria, three survived. The outlook for postoperative renal failure was grim. Of the 12 patients in whom oliguria was initiated by an operation and not caused by a hemolytic transfusion reaction, 4 recovered. The majority of the fatalities (eight in this group) followed aortic grafts, and two of these patients had multiple occlusions of the renal arteries. The two patients with eclampsia and the two with postabortional sepsis, although they were severely ill, recovered. One patient had been asphyxiated while at work in a chemical tank which was accidentally filled with nitrogen instead of air. He recovered after 18 days of oliguria.

Further Analysis of the Patients Who Died.—In retrospect it is nearly always possible to determine whether or not on admission a patient was irrecoverably ill or potentially recoverable. In this series 14 patients are considered to have been irrecoverably ill from renal disease, underlying disease, or complications of either (Table 2). It is difficult to imagine how the best of medical management, including dialysis, could have saved these patients at the present stage of our knowledge.

In four cases diagnoses were made only after dialysis. One patient had hepatic stones with liver-cell necrosis. One had necrotizing papillitis, and two had carcinomas leading to obstruction of the ureters. Dialysis thus prolonged life until the diagnosis of irrecoverable disease was established.

The concept of the potentially recoverable patient was introduced because it is in this category that future improvement of management and diagnosis should be sought. The following four patients qualified for the classification "potentially recoverable."

One patient died of cardiac arrest due to potassium intoxication on the 15th day of oliguria while cut-downs were being done for the third treatment with the artificial kidney. We had failed to anticipate the rapid rise of potassium.

One patient with a perforated hiatal gastric ulcer and empyema died on the 13th day after the onset of oliguria when a

TABLE 3.—*Immediate Causes of Death in Eighteen Patients* *

	Cause of Death	Total	Clinical Problem †	
			Potentially Recoverable	Irrecoverable
Cardiac	Cardiac arrest	1	(*a*)	
	Cardiac failure	0		
	Myocardial infarction	0		
	Renal failure	7		XXX (*d, d, e, g*)
	Potassium intoxication	1	(*a*)	
	Sepsis	4	(*b*)	XXX
Pulmonary	Edema	2	X	X
	Pneumonia	1		X
	Mucus retention	0		
	Embolus	2		X (*c*)
	Other	9	X	XXXX (*e, f, h, h*)

* This Table corresponds to the upper right side of the punch card (Fig. 1).

† X indicates the immediate cause of death was recognized (15 times); (*a, b, c, d, e*), the immediate cause of death was unrecognized (5 times); (*f, g, h,*), the diagnosis was made only after dialysis (4 times); (*a*), cardiac arrest is also listed as potassium intoxication; (*b*) ligated midjejunum; (*c*) pulmonary fat embolus (after surgical repair of fractures); (*d*) emboli in renal arteries (after graft); (*e*) necrotizing angiitis; (*f*) hepatic duct stones with liver-cell necrosis; (*g*) necrotizing papillitis; (*h*) carcinoma of (1) pancreas, (2) retroperitoneum.

saphenous catheter was pulled out during the night and bleeding occurred. Death occurred when the urine output had reached 1200 ml/24 hours. We do not think that we could have treated this severely ill child without an indwelling high saphenous catheter, but it should have been made more secure.

One patient was a victim of a stabbing, with perforation of the diaphragm and stomach, and had localized peritonitis and empyema. The laparotomy wound dehisced and was repaired; it was not recognized that a stay suture obstructed the jejunum.

One patient had a suprapubic prostatectomy. He died of unknown causes on the second day following dialysis. There was a high temperature. The urine output had reached 1180 ml/24 hours. Postmortem examination was not granted. This patient was listed as potentially recoverable to give him the benefit of the doubt.

Immediate Causes of Death (Table 3).—It is important to know the immediate causes of death, since their future elimination will either save life or prolong it.

Myocardial infarction and cardiac failure are listed on the punch card because they occur in acute renal failure, although they did not happen in this series. Pulmonary complications in acute renal failure are always serious and were considered to be the mechanism of death in five cases; one patient might have recovered had she come earlier.

In two other cases death might have been prevented had the cause been recognized (potassium intoxication and obstruction of jejunum due to a suture; both have been mentioned). In this series the recovery rate could at most have been improved from 52% to 63% if no errors in diagnosis, management, or judgment had been made.

Survival Time.—Of the 18 patients who died, only 2 died within 24 hours. The average survival times were the same (7.7 and 7.6 days, respectively) regardless of whether the patients were potentially recoverable or not. In no case was death hastened by dialysis.

Degree and Duration of Oliguria.—No patient developed diuresis before the fifth day (Table 4). Diuresis || began between the 5th and 10th day in patients with the following conditions: bichloride of mercury poisoning, staphylococcal enteritis, eclampsia, postoperative oliguria (2) and post-traumatic oliguria (2), and obstruction of the ureters

|| The beginning of diuresis is arbitrarily chosen as 1500 ml/24 hours.

TABLE 4.—*Duration of Oliguria Until Diuresis* *

		Total	Dead	Survivors
Total days of oliguria until urinary output reaches 1,500 ml.	<5	0	0	0
	5-10	9	1	8
	11-20	13	2	11
	>20	2	1	1
No diuresis: Urine output never 1,500 ml.		14	14	0

* This Table is taken from the left side of the punch card. The beginning of diuresis is arbitrarily chosen as 1,500 cc/24 hours. Diuresis occurred in four patients who nevertheless later died.

due to bladder carcinoma.¶ Oliguria lasting longer than 10 days occurred in all cases that commonly have severe intravascular hemolysis: in all six patients having had transfusion accidents, in two with septic abortions, and in one of the two eclamptic patients. This experience may be helpful in estimation of the duration of oliguria in future cases with intravascular hemolysis.

Severer oliguria took longer to proceed to diuresis. In the six patients who recovered notwithstanding severest oliguria (known urine outputs of less than 100 ml. per day), it took longer than 10 days for diuresis to occur. In contrast, in four of the six patients who recovered from less severe oliguria (known oliguria between 100 ml. and 500 ml/24 hours) diuresis occurred before the tenth day. The only three patients who died after attaining a urinary output of 1500 ml., came from this 100 to 500 ml. category. From our data it seems obvious that the smaller the daily urine output at the onset, the longer it takes for diuresis to occur; this was not formerly recognized.

As the number of patients with severe and less severe oliguria was equally divided between the survivors and the nonsurvivors (Table 5), the degree of oliguria at the onset cannot be used as a prognostic sign. In patients with ultimately fatal outcome, severe oliguria did not preclude long survival.

¶ This patient was listed here as recovered (improved) because his renal function recovered and he went home after treatment although the underlying disease was irrecoverable.

TABLE 5.—*Degree of Oliguria Before Dialysis Correlated with Death and Survivals* *

	Total	Dead	Survivors
<100 ml. urine/day	12	6	6
100 ml. urine/day	11	5	6

* This Table is taken from the left side of the punch card (Fig. 1). The number of patients with severe and less severe oliguria is equally divided between the survivors and the nonsurvivors; thus, the degree of oliguria at the onset cannot be used as a prognostic sign.

Long-lasting oliguria need be no reason for despair. One patient recovered although it took over 20 days (Table 4). Alwall [9] reported a recovery after 60 days. On the other hand, three patients died notwithstanding diuresis of 1500 ml. at one time.

Chemical Efficiency of Dialysis.—The average predialysis urea in the 11 patients with blood urea over 300 mg/100 ml. was 385 mg/100 ml. It was reduced to 131 mg/100 ml. at the end of dialysis.

The HCO_3^- was restored to between 20 and 30 mEq. per liter (Table 6) in all but five patients, while in one patient it was corrected from 6 to 18 mEq. per liter and in four it remained unaltered between 17 and 20. In all but two patients the Cl^- was restored to between 90 and 110 mEq. per liter (Table 6). In one it reached 88; in another, 85 at the end of dialysis. Serum Na^+ was restored to between 130 and 145 mEq. per liter in 32 patients (Table 6). In five with initial serum Na^+ of 114 to 119, it was purposely not corrected to more than 124 to 128 mEq. per liter. We usually do not raise a low serum Na^+ suddenly.

The initial values of blood urea and the initial abnormalities in electrolytes do not determine patients' recovery (Table 6). Dialysis corrects the initial chemical abnormalities so effectively that they play no role in the eventual occurrence of death. The outcome is rather determined by presence of irrecoverable disease (38% of our cases).

Correlation Between Na^+ and HCO_3^-.—When the initial serum Na^+ was low, the HCO_3^- was also low (Table 7), except in three patients in whom the HCO_3^- was

TABLE 6.—*Chemical Data in Thirty-Eight Patients, Correlated with Recovery and Death* *

			Total	Recovered	Died	Potentially Recoverable
Blood urea, mg. %	Before	100	0	0	0	0
		100-300	27	14	13	3
		300	11	6	5	1
	End	100	20	10	10	3
		100-200	18	10	8	1
		200	0	0	0	0
Urea removed, gm.		50	5	2	3	1
		50-200	33	18	15	3
		200	0	0	0	0
HCO_3^-, mEq/L.	Before	10	3	3	0	0
		10-20	21	10	11	4
		20-30	12	6	6 †	0
		30	1	1	0	0
	End	20-30	33	16	17	4
Cl^-, mEq/L.	Before	90	16	6	10	1
		90-110	21	14	7	2
		110	1	0	1	1
	End	90-110	36	20	16	4
Na^+	Before	125	11	5	6	1
		125-145	24	14	10	2
		145	3	1	2	1
	End	130-145	32	18	14	3
K^+, mEq/L.	Before	3.5	6	5	1	1
		3.5/5.5	23	11	11 †	2
		5.5/7.0	7	4	3	1
		7.0	1	0	1	0
	End	3.5/5.5	38	20	18	4

* This table is formed by combination of the lower right side and right bottom of the punch card, correlated with survival and recovery. Main conclusion is that chemical abnormalities are well corrected. The patients who died later, irrecoverable or potentially recoverable, did not have chemical changes in their blood that were more seriously abnormal than in those patients who recovered.

† One not determined.

normal and in one patient (a man with profound Cl^- loss after a gastric operation) in whom it was elevated. When the HCO_3^- was low, the serum Na^+ was nearly always low. There were only 3 patients out of 21 who had an HCO_3^- between 10 and 20 mEq. per liter and a serum Na^+ of more than 145 mEq. per liter. Thus, sodium lactate or bicarbonate usually can be administered to correct a low HCO_3^- without unduly increasing the serum Na^+. Administration of Na^+ in any form to patients in uremia is, however, rarely indicated.

TABLE 7.—*Correlation Between Serum Sodium and Bicarbonate Before the First Dialysis* *

	Bicarbonate			
Na^+, mEq/L.	<10	10-20	20-30	>30
<125	2	5	3	1
125-145	1	13	10	0
>145	0	3	0	0

* This Table is taken from lower right side of the punch card. Low serum sodium is often associated with low HCO_3^-.

Blood Urea.—We have previously seen that there was no correlation between the severity of oliguria and the survival rate (Table 5). The height of the initial blood urea does not influence it either (Table 6). Of the 11 patients with initial blood ureas higher than 300 mg/100 ml., 6 (or 54%) recovered, and of these only 2 needed 10 or more days to recover. Of the 27 patients with blood ureas between 100 and 300 mg/100 ml., 14 (or 52%) recovered, and

9 of these patients required 10 or more days to recover. There was no correlation between the degree of oliguria and the height of blood urea. Of the 12 patients with urine outputs of less than 100 ml. per day, only 3 had blood ureas over 300 mg/100 ml. Nor was there a correlation between the duration of oliguria prior to dialysis and the height of the blood urea. In this series patients dialyzed early had no better chance for recovery than those dialyzed later, probably because the more seriously ill patients were dialyzed earlier.

Clinical Symptoms.—The clinical symptoms, as shown on the bottom of the punch card (Fig. 1), have been correlated with HCO_3^- and blood urea. A blood urea higher than 300 mg/100 ml. coincided more often with coma than did a low HCO_3^- (less than 10 mEq. per liter). Of the patients with blood ureas greater than 300 mg/100 ml., only 1 of 11 was severely acidotic, and this patient was restless, not comatose. On the other hand, of the five patients in coma, three had blood ureas greater than 300 mg/100 ml. and none was severely acidotic. All three patients with severe acidosis were restless and/or confused. One would have expected the patients with high blood ureas also to be most severely acidotic; this was not found.

Only one patient was psychotic and had hallucinations. He had alkalosis following a pyloric obstruction.

Improvement of mental disturbance by dialysis was evident: Of the 5 patients in coma, 4 improved; of the 14 patients with confusion and restlessness, 12 improved; of the 16 drowsy patients, 13 improved; the hallucinating psychotic patient also improved. As we know from previous experience that too rapid dehydration during dialysis may lead to increased confusion, this was avoided.

Seven of the ten patients with twitching had HCO_3^- less than 20 mEq. per liter. The three patients with twitching who had normal HCO_3^- had blood ureas of 200, 240, and 312 mg/100 ml. Acidosis, therefore, cannot be the sole explanation for uremic twitching (Mg^{++} determinations were not available). The twitching disappeared after dialysis in all 10 patients.

The 11 patients with Kussmaul type respiration all had HCO_3^- of less than 20 mEq. per liter, so in this small series the clinical observation of Kussmaul respiration justified the assumption that the HCO_3^- is low. Dialysis brought improvement in 9 of the 11 patients.

Vomiting is clearly not related to acidosis: Five of the eight patients who vomited had normal or high HCO_3^-. The chloride loss may have caused compensatory rise of HCO_3^-. Indeed, three of the nonacidotic patients with vomiting had chlorides of less than 90 mEq. per liter (45, 83, and 88 mEq. per liter).

Blood Pressure Changes During Dialysis. Temporary changes in blood pressure have often been described. Temporary increase of systolic pressure by more than 50 mm. Hg occurred four times in 38 dialyses. Increase in diastolic pressure of more than 20 mm. occurred four times. Temporary decrease of systolic pressure by more than 50 mm. occurred five times; decrease in diastolic pressure by more than 30 mm. also occurred five times. However, these changes must be seen against the background of the preexisting blood pressures. It then appears that there was no *decrease* in blood pressure in any patient who was already hypotensive. Also there was no *increase* in the blood pressure of any patient who was already hypertensive. The changes as a rule were in a desirable direction. For example, a persistent increase occurred in one patient whose blood pressure prior to dialysis could not be maintained even with *l*-norepinephrine (levarterenol [Levophed]). A lasting decrease in blood pressure occurred in the only patient with severe hypertension. Two (nonhypertensive) patients were dialyzed notwithstanding a seemingly hopeless condition. Temporary falls in blood pressure occurred but were corrected.

Postdialysis Oliguria.—After dialysis the urine output remained unchanged in 11, in-

creased in 10, and decreased in 11 instances. In the remaining six predialysis urine output was unknown. The 24-hour urine volume sometimes decreased insignificantly (from 20 to 12), but sometimes it decreased from 300 to 60 ml. The relative decreases as a rule lasted but a single day, as was demonstrated by Aoyama and Kolff.[6] Of the 11 patients in whom the urine volume decreased, 3 survived and 8 died; all 8 were later found to have irrecoverable disease. In some of them the decrease persisted until death. Although it has caused no serious consequences, the relative postdialysis reduction of urine volume is considered a disadvantage of our present techniques of dialysis.

Bleeding During Dialysis.—Fourteen of thirty-eight patients bled before, during, or after the first dialysis. As a rule it was more a nuisance than a serious event, and most of it was oozing from cut-down sites. One patient having cirrhosis and elevated prothrombin time bled from a postoperative prostatic bed. He is the only one whose bleeding approached 1 liter. One patient with, in retrospect, irrecoverable disease (necrotizing angiitis) and severely uremic had generalized capillary hemorrhages throughout the body before, during, and after dialysis.

Regional heparinization was employed in only one patient of this series and only during the second and third dialyses. The patient was bleeding from the gastrointestinal tract prior to these dialyses, and though bleeding continued unaltered during both dialyses it was never out of control.

Summary

Thirty-eight patients in acute renal failure were treated with twin-coil kidneys as part of an integrated program of medical management at the Cleveland Clinic in 1957. Clinical and chemical data were analyzed with specifically designed McBee marginal punch cards which also allot sufficient space for numerical data and a short history of the patient.

Over-all recovery rate was 52%. Of 13 patients older than 60 years, 5 recovered. Of six patients with hemolytic transfusion reactions, four recovered. The patients with eclampsia and postabortional sepsis recovered.

Of the 18 patients who died, 14 proved in retrospect to have irrecoverable disease. Of the remaining four whose disease was potentially recoverable, death in three was attributed to errors in management or diagnosis. In the present series, the recovery rate could at most have been improved from 52% to 63%. Pulmonary complications often led to death (five cases). Earlier improvement of the patient's condition by dialysis and ultrafiltration should enable us to make better diagnostic studies.

Urine output of 1500 ml/24 hours was arbitrarily defined as the beginning of the diuretic phase. The smaller the urine output at onset, the longer it took before diuresis was established. However, outlook could not be predicted on the basis of more or less than 100 ml. output per 24 hours, and relatively long duration of oliguria was no reason for despair. The initial height of blood urea did not reflect the degree of preceding oliguria and was not reflected in the ultimate outcome or in the days required for recovery. All of these apparent contradictions can be explained on the basis of the fact that dialysis reverted chemical abnormalities to near normal, and the ultimate outcome depended mainly on the fact that 38% of our patients proved to have irrecoverable disease.

Low initial serum Na^+ usually paralleled low HCO_3^-. A high blood urea was associated more often with coma than was low HCO_3^-, but the three patients with severe acidosis were restless and/or confused. A very high blood urea and a very low HCO_3^- did not usually occur together in the same patient.

Mental changes improved after dialysis as follows: coma, 4 of 5; restlessness, 12 of 14; drowsiness, 13 of 16. Twitching improved in all 10 cases. Twitching occurred

often with low HCO_3^-, although acidosis is not the only explanation.

Kussmaul respiration improved in 9 of 11 patients, all of whom had low HCO_3^-. Vomiting was not related to low HCO_3^- and improved after dialysis. Blood pressure changes during dialysis and relative urinary depression have been inconsequential. Bleeding during dialysis was more of a nuisance than a serious problem, and it can now be avoided by regional heparinization.

The Cleveland Clinic, 2020 E. 93d St. (6) (Dr. Kolff).

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An Analysis of Some Features of Renal Tubular Dysfunction

CHARLES H. BURNETT, M.D., and T. FRANKLIN WILLIAMS, M.D., Chapel Hill, N. C.

A number of renal disorders which differ from those most commonly seen in clinical medicine have received wide attention during the last three decades. Prominent among these is a group of diseases or syndromes characterized by abnormalities which can be traced primarily to impairment of one to several functions of the renal tubules, including those associated with abnormalities of cation excretion, especially of potassium and calcium. It is the purpose of this report to consider some current concepts of the abnormal mechanisms operating in some of the better-studied syndromes in this group of renal diseases, to suggest possible relationships between some of them, and especially to attempt to identify areas where further experimental observations are necessary. Management in most instances has become fairly well standardized; one would anticipate little change until more fundamental understanding of their pathogenesis is achieved. No attempt will be made to discuss the syndromes completely, since numerous recent reviews are available and are cited in the references.

Several characteristics warrant separation of this smaller group of disorders from the more commonly encountered chronic renal insufficiency or failure. Chronic glomerulonephritis, pyelonephritis, and nephrosclerosis are the commonest precursors in the latter group and are characterized by both progressive destruction of total nephrons and marked anatomical and functional disruption of remaining nephrons. It is this group which is usually referred to as chronic Bright's disease. In the group of tubular disorders to be considered, azotemia and impairment of glomerular filtration rate are not prominent early features although filtration rate may decrease markedly late in the course, presumably as a result of secondary effects of the primary tubular damage. Some of these conditions are characterized by one or only a few discrete tubular abnormalities of functions of the kidneys. Most of them, if accurately defined, offer distinct therapeutic possibilities, which are often far more rewarding than in chronic Bright's disease. Finally, the discrete nature of most of the lesions provides a fruitful field for correlation of normal and abnormal renal function.

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From the Department of Medicine, University of North Carolina School of Medicine.

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Familial Hypophosphatemia and Vitamin D-Resistant Rickets

General Characteristics.—This is a specific disorder, presumably hereditary, which produces rickets in children and responds to large but not small doses of vitamin D. In at least two large kindreds recently studied the mode of inheritance has been found to follow a sex-linked dominant pattern if hypophosphatemia, as well as the presence of skeletal abnormalities, was used as a criterion of the disease. To my knowledge, nothing is known of the pathologic anatomy of the kidneys.[1,2]

Metabolic Features.—These are (1) hypophosphatemia usually associated with a normal serum calcium but elevated alkaline phosphatase in children (normal in adults),

(2) a probable gastrointestinal defect in the absorption of calcium and phosphorus, and (3) diminished reabsorption of phosphate from the glomerular filtrate without other obvious defects of renal function. The maximal ability of the renal tubules to reabsorb phosphate (Tm_P) was measured in eight hypophosphatemic adults of one kindred, both with and without skeletal deformities, and was found to be reduced in each instance. This renal abnormality could be due solely to a single intrinsic renal tubular defect or to secondary hyperplasia of the parathyroid glands.[1] It is possible that both features may exist.

Renal Glycosuria

In the context of this discussion renal glycosuria needs mention only to emphasize that it is usually benign, that the renal defect is limited to a reabsorptive defect for glucose, and that it may be inherited.

Cystinuria

General Characteristics.—This is a hereditary condition involving recurrent calculus formation accompanied by abnormal excretion of cystine, lysine, arginine, and ornithine.[3] Renal damage occurs only as a consequence of calculus formation. The familial distribution is typical of either a Mendelian recessive character in which the homozygote, carrying a rare recessive gene, has abnormalities in reabsorption of all four of the amino acids, or an "incomplete recessive cystinuria." In the latter group three patterns have been demonstrated: (1) increased excretion of all four amino acids, (2) only cystinuria and lysinuria present, and (3) no amino-aciduria. The incidence of calculus formation which usually occurs among homozygous persons—those with increased excretion of all four amino acids—has been estimated at about 65%.

Metabolic Features.—Sharp differentiation should be made between cystinuria and amino-aciduria which occur in Fanconi's syndrome and those which occur in other disorders (see below). The serum concentration of the amino acids excreted in cystinuria is normal or low. The defect, therefore, in cystinuria seems to be solely impairment of the ability of the renal tubules to reabsorb the specific amino acids (cystine, lysine, arginine, and ornithine).

Fanconi Syndrome

General Characteristics.—The earliest reports of this syndrome described a hereditary error in metabolism in children manifesting rickets and other disturbances in growth and a variety of renal functional abnormalities.[4] Subsequent reports have demonstrated that the hereditary form has usually been associated with cystinosis (Fanconi-Lignac syndrome), an abnormality in cystine metabolism leading to deposition of cystine crystals in many organs, especially the reticuloendothelial system and occasionally the kidney. In addition, however, hereditary forms in both children and adults without cystinosis occur.[5-10] To date this syndrome has also been reported in association with heavy-metal poisoning, glycogen-storage disease, hepatolenticular degeneration, and multiple myeloma.[6,11-13] Experimentally the syndrome has been produced by administration of maleic acid.[12] The prognosis is in general poor, and treatment is only moderately satisfactory although reversal following massive vitamin D therapy has been reported.[7]

A peculiar renal lesion, demonstrable by microdissection and characterized by shortening of the proximal tubule and replacement of the first part of the proximal tubule by a narrow neck for about one-third of its length, has now been demonstrated in 8 of 11 cases of cystinosis and in 2 cases (1 an adult) with Fanconi syndrome without cystinosis.[15]

Metabolic Features (Table 1).—Impairment of tubular reabsorption of phosphate, glucose, and amino acids from the glomerular filtrate is the usual and distinctive pattern. Rare instances of impairment of only phosphate and glucose[16] or of only amino acids and glucose[17] have been reported.

TABLE 1.—*Metabolic Characteristics of the Fanconi Syndrome*

Serum
Glucose and amino acids normal
Hypophospatemia
Normal serum calcium
Hypopotassemia
Acidosis, frequent
BUN, normal or slight elevation
Urine and Kidneys
Glycosuria
Amino-aciduria
Phosphaturia
Alkaline urine
Renal function frequently depressed
Nephrocalcinosis *absent*

Serum glucose and amino acid levels are normal. It should be emphasized that the defect in amino acid reabsorption, in contradistinction to that present in cystinuria, involves impaired reabsorption of a wide spectrum of amino acids and, further, that cystinosis is not the same condition as cystinuria. Hypophosphatemia is often, though not invariably, present and usually accompanied by osteomalacia, which is resistant to vitamin D. Although the low serum phosphorus is considered to be an important factor in the pathogenesis of the osteomalacia, the part that the increased excretion of glucose and amino acids play is unclear.[18] Acidosis and excessive excretion of potassium are extremely common; the latter defect frequently leads to serious hypopotassemia.

Attempts to formulate the pathogenesis of Fanconi syndrome lead to certain tentative conclusions and a number of inconsistencies. A variety of etiologies produces the impairment of tubular transport of phosphate, glucose, and amino acids. It is possible that in each instance development of the syndrome is secondary to a variety of factors inducing impairment of these systems. Thus, in cystinosis the renal lesions have appeared after deposition of cystine crystals elsewhere in the body.[7] As mentioned above, the syndrome may follow heavy-metal poisoning (especially lead),[11] Wilson's disease (in which an abnormality of copper metabolism is now clearly established),[12] and multiple myeloma.[13] These observations suggest, but by no means prove, that all cases may be the result of damage to the renal tubular cells from a variety of agents. Of considerable interest is the possible relationship to vitamin D. Amino-aciduria occurs in infants with vitamin D-deficiency rickets and disappears with treatment with vitamin D.[8] Reversal of Fanconi syndrome has resulted from massive vitamin D therapy.[7] Harrison suggests that there may be some significance to this observation that vitamin D can influence amino-aciduria in association with phosphaturia.[8] The fact that amino-aciduria does not usually occur in vitamin D-resistant rickets is puzzling in this context.[1] The cause of the acidosis and excessive excretion of potassium is essentially unexplained. Possibly the same factors are operating as in renal tubular acidosis (see below). The osteomalacia when present is probably initiated by the phosphaturia and hypophosphatemia. Nephrocalcinosis does not occur in this syndrome, in contrast to its high incidence in renal tubular acidosis (see below).

Renal Tubular Acidosis

General Characteristics.—This syndrome may occur in children or adults and is characterized by weakness, gait disturbances, and bone pain. The weakness is to a large degree the result of potassium deficiency, a common feature of the disease. The gait disturbances and bone pain are the result of osteomalacia. The designation of this disorder as renal tubular acidosis is possibly an unfortunate one.[19] However, continued use of this term is probably as satisfactory as any until better understanding of the pathogenesis of this group of disorders is achieved. Polyuria, polydipsia, persistent dehydration, and renal colic are common. A familial incidence has been described in a number of cases.[20-23,39] Roentgenologically, osteomalacia with pseudofractures and demineralization usually are present. Visible (by x-ray) nephrocalcinosis or nephrolithiasis or both are present in a high percentage of cases. Diagnosis can be established positively only by demonstration of the

TABLE 2.—*Metabolic Characteristics of Renal Tubular Acidosis*

Serum
Acidosis
Hyperchloremia
Hypophosphatemia (occasionally normal phosphorus)
Normal or slightly low serum calcium
Azotemia, absent or minimal
Hypopotassemia, frequent
Urine and Kidneys
Alkaline urine
Proteinuria
Moderate reduction in renal function
Isosthenuria
Nephrocalcinosis

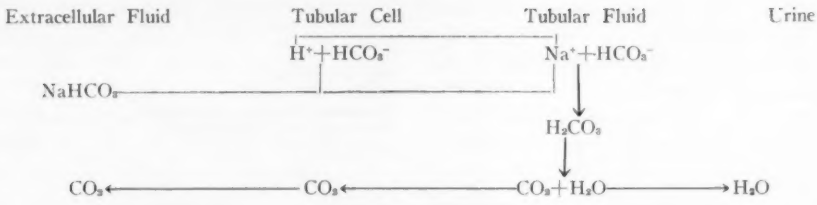
characteristic metabolic and renal functional abnormalities discussed below.

The few pathologic anatomic studies available are inconsistent.[24-26] The commonest findings have been deposits of calcium in the area of the distal convoluted tubule and the collecting tubules. Rarely, degenerative changes in the proximal tubules have been described.

Metabolic and Renal Functional Features (Table 2).—These are well established. The sequence of abnormal renal events in the production of these features is much less clear, and the data on studies of reported cases are often conflicting. Explanation of at least four aspects of the metabolic abnormality is necessary for better understanding of the pathogenesis. These are (1) the acidosis, (2) the usual finding of hypophosphatemia accompanied by osteomalacia, (3) the nephrocalcinosis, and (4) the hypopotassemia. Glycosuria and aminoaciduria do not occur.

Acidosis: Data from balance studies presented by Albright's group in 1946 (viewed in the light of studies by Pitts reported at about the same time), demonstrating the secretion of H^+ by the renal tubule, can now be interpreted as suggesting that formation of hydrogen ion and ammonia are both impaired in this syndrome.[24,27] Subsequent studies demonstrated that it was possible significantly to increase hydrogen ion secretion, as reflected by titrable acidity, by intravenous infusions with buffered phosphate solution.[28-30,40] However, the response as compared to normal control subjects was not maximal. These observations originally led Latner and Burnard to the suggestion that proximal tubular bicarbonate reabsorption was impaired.[28] However, in two independent studies it has been demonstrated that loading with bicarbonate results in a marked increase in the amount of bicarbonate reabsorbed and little increase in the quantity of excreted bicarbonate.[29,30] These observations argue strongly against impairment of bicarbonate reabsorption as the primary abnormality responsible for the acidosis. Mudge, in a recent thoughtful analysis of existing data, has proposed that the apparently conflicting data can be reconciled if they are evaluated in terms of two functions: the total amount of hydrogen ion added to the urine and the gradient of hydrogen ion against which this secretion occurs.[6]

In formulating such a hypothesis it is advantageous to digress to point out briefly a number of current concepts of mechanisms of acidification of the urine in the normal and to consider how impairment of these mechanisms in renal disease of any type may produce acidosis. The highest gradient against which hydrogen ion can be transported in the normal human kidney is limited by a urinary pH of 4.5. Most of the hydrogen ion involved in tubular transport is exchanged for sodium ions. The pH of the urine is a measurement of the quantity of free hydrogen ions contained in it, but the concentration of buffers in the urine markedly influences the pH. The most important of these buffers are bicarbonate and phosphate. The pH of the urine in subjects with renal impairment must therefore be interpreted with caution, for a small quantity of dissociated acid in a poorly buffered urine will cause significant lowering of pH. Similarly, a urine of relatively high pH does not necessarily indicate low hydrogen ion production. In the transport of bicarbonate to venous blood it is probable that the bicarbonate filtered is not that which reaches venous blood:



That quantity of carbonic acid which is dehydrated and recycled as carbon dioxide reflects a part of hydrogen ion production which is transported into tubular fluid without any gain in hydrogen ion in the urine per se. Sodium bicarbonate, nonetheless, has been added to the reabsorbate and participates in combatting the tendency for serum bicarbonate to fall as a consequence of exogenous and endogenous acids. In addition, hydrogen ion exchange contributes to the maintenance of acid-base equilibrium by incorporation with buffers to form undissociated acid and probably by the combination of free hydrogen ion with ammonia (which diffuses from the tubular cells) to form the ammonium ions of the urine.[31] It is therefore true that acidosis in any kind of renal disease is tubular in origin and, in the last analysis, can be ascribed to primary or secondary abnormalities in the transport of hydrogen ion by the renal tubular cell. In achieving a steady state in acidosis due to renal disease, reabsorption of the dimished filtered load of bicarbonate requires a smaller quantity of hydrogen ions and equilibrium may be established in a manner somewhat comparable to that achieved for urea excretion in azotemia and renal failure.[19]

In regard to the syndrome of renal tubular acidosis, published data would be reconciled if it is assumed that there is an impaired ability to transport hydrogen ions against a concentration gradient. With infusion of phosphate or bicarbonate, hydrogen ion transport could be markedly increased with little change in gradient. This same reasoning would explain inadequate ammonium response, because presumably ammonia synthesis, which is stimulated by increasing acidity of tubular fluid, is decreased by virtue of the relatively high tubular fluid pH. Further, the well-established therapeutic benefit of alkalizing solutions is explained by this hypothesis. The possibility that a carbonic anhydrase inhibitor, or some defect in the carbonic anhydrase enzyme system, could be responsible for initiating the sequence of events observed in renal tubular acidosis is discussed below. It should be conceded at once, however, that, although this provides an attractive hypothesis, proof of any such defect awaits further investigation.

Hypophosphatemia: Most patients with this syndrome have a low serum phosphorus. This finding was originally ascribed to the absence of significant diminution in glomerular filtration rate plus increased parathyroid secretion which was stimulated as a result of urinary loss of calcium. Serum levels of phosphorus under circumstances of marked reduction in glomerular filtration rate rise as glomerular function becomes progressively impaired.[32] In tubular acidosis, although there may be some diminution in filtration rate, such reduction is usually slight. Whether, however, the hypophosphatemia is due to increased parathyroid hormone (Parathormone) activity on normal renal tubules or whether there is an intrinsic tubular defect should be reexamined. Measurement of tubular maxima for phosphate under varying conditions would be interesting. The fact that in treatment of the disease, once the bone lesions are remineralized after administration of vitamin D, alkalies alone will prevent further demineralization argues against an intrinsic renal defect for reabsorption of phosphate unless correction of the acidosis simultaneously corrects the defect in phosphate

absorption. In normal people, increased phosphate excretion produces a lower urinary pH. There is no explanation for this phenomenon. However, patients with this syndrome who were infused with phosphate have shown little decrease in pH.[28,29,40]

Nephrocalcinosis: In a majority of patients either nephrocalcinosis or nephrolithiasis, or both, are present. Balance studies have clearly demonstrated in both normal subjects and patients with renal tubular acidosis that an excess of exogenous acids increases the excretion of calcium. Further, with equivalent acid loads induced by ammonium chloride, excretion of calcium and the degree of acidosis were greater in a patient than in a control.[24] From these and other studies the presence, at least intermittently, of hypercalcuria resulting from the acidosis seems clearly established. Although nephrocalcinosis occurs in a variety of pathologic conditions, including uremia and acidosis from the commoner types of renal disease, the incidence in this syndrome seems more than fortuitous. Analysis of this aspect of the disease is rendered especially difficult because of the paucity of information concerning the mechanisms by which calcium normally is excreted by the kidneys.

There is one possible explanation for the nephrocalcinosis which has been suggested by Harrison and warrants further study.[33] In an infant with congenital renal acidosis, studied by him, citrate in the urine was too low to be measured, and this condition persisted after correction of the acidosis. There is considerable evidence that citrate is important in increasing the solubility of calcium in the urine because it forms undissociated complexes with that cation. In normals, urinary citrate increases following administration of alkalies, vitamin D, and parathyroid extract. Calcium excretion also increases after administration of the last two, although citrate and calcium output do not necessarily parallel each other. The carbonic anhydrase inhibitor, acetazolamide, administered to rats reduced urinary citrate excretion to very low levels.[34] This substance also produces an alkaline urine which is accompanied by a systemic hyperchloremic acidosis, a picture similar to that obtaining in renal tubular acidosis (Table 3). In the studies by Harrison, acetazolamide also inhibited the citraturia which followed cation excess and vitamin D in control animals. Precipitation of calcium salts was observed in the lower urinary tract of these animals. On a diet resembling cow's milk this precipitation was at the corticomedullary junction, whereas on a diet low in phosphate and high in calcium calcified plaques were formed at the tips of the papillary ducts, with the formation of calculi in the pelvis.

TABLE 3.—*Features Common to Renal Tubular Acidosis and Carbonic Anhydrase Inhibition*

Metabolic acidosis
Alkaline urine
Hyperpotassuria and hypopotassemia
Reduced urinary citrate excretion
Nephrocalcinosis

Further studies in humans are clearly necessary, but the possibility of relationship between impaired citrate excretion and nephrocalcinosis in renal tubular acidosis must be seriously entertained. The possibility of deficiency of carbonic anhydrase in renal tubular acidosis has been rejected on the grounds that patients who have received acetazolamide have produced an increase in bicarbonate excretion typical of carbonic anhydrase inhibition.[35] However, recent studies necessitate reevaluation of this conclusion.[36] In normal dogs the response to acetazolamide showed a diminishing effect of the drug on the reabsorptive process as plasma bicarbonate was reduced. Before abandoning the possibility of impairment of carbonic anhydrase activity, or of the presence of an inhibitor of this substance in tubular acidosis, comparative studies must be carried out between normal subjects and patients with this disease to ascertain whether there are quantitative differences in response to acetazolamide under varying degrees of acidosis. Carbonic anhydrase activity of red cells and renal tissue obtained from renal biopsy in patients

with this disease would also be most informative.

Hypopotassemia: It has already been stated that the symptomatology of this syndrome is often predominatly related to interference with neuromuscular function resulting from potassium deficiency. The pathogenesis of this aspect of the disease is also unsettled.

It is generally agreed that in the presence of normal renal function the majority if not all of the potassium which appears in the urine is secreted by the distal segment of the renal tubule in exchange for sodium from the renal tubular fluid. There is good evidence that in the presence of a strong stimulus for reabsorption of sodium the exchange of sodium for potassium is enhanced. Further, it has been demonstrated that rates of secretion of hydrogen and potassium ion are inversely related under a number of conditions.

The exact explanation of the excessive excretion of potassium in this syndrome, or indeed in any instance of renal insufficiency which produces excessive loss of potassium in the urine, is not clear. Accentuation of the acidosis in this syndrome clearly accentuates potassium loss.[24] Presumably there is a stimulus for sodium conservation which is partially achieved by exchange of sodium for potassium. Further, inasmuch as hydrogen ion exchange is compromised more than potassium exchange, this conservation is at the expense of body potassium. The frequency and severity of the hypokalemic episodes so characteristic of this disorder may be a function of the relatively normal glomerular filtration rate usually present. Thus, although hypokalemia is not uncommon in renal failure due to those conditions associated with a low glomerular filtration rate—chronic glomerulonephritis, pyelonephritis, etc.—it is also extremely common for hyperkalemia to supervene as renal function progressively deteriorates. This latter feature must be due to the fact that total renal tubular function finally becomes inadequate to effect sufficient potassium secretion to maintain normal serum potassium levels. In renal tubular acidosis, it has been hypothesized that the defect is a functional one involving, among other tubular defects, an inability to transport hydrogen ion. Sodium-potassium exchange, however, is presumably not impaired, or at least not to the same degree as is true of hydrogen ion transport. The presence of a normal or only moderately reduced glomerular filtration rate implies a relatively adequate number of nephrons capable of secreting large quantities of potassium. The possible similarity of the mechanism of hypokalemia in this syndrome to that occurring after carbonic anhydrase inhibition raises again the question whether this syndrome may be in some way related to impairment of carbonic anhydrase activity.

In contradistinction to many other conditions of potassium depletion, administration of sodium bicarbonate results in a fall in urinary potassium excretion. This phenomenon could be interpreted as due to diminution in stimulus for retention of sodium following repletion of that cation.

Other Renal Defects.—A concentrating defect is a frequent but not invariable feature. At least two explanations for this finding can be given. First, the frequent episodes of potassium depletion would be expected to be accompanied by an inability to concentrate the urine appropriately.[37] Second, the localization of the nephrocalcinosis in the medullary portion of the kidney could represent damage to both the thin limbs and the collecting ducts, both of which are now known to be concerned in experimental animals with concentration and dilution of the urine.[38] Two patients who could concentrate their urine had no nephrocalcinosis visible by x-ray in our original series.[24]

Treatment.—Therapy with vitamin D and alkalies has been quite satisfactory, with discontinuance of the vitamin D after the osteomalacia has healed. Prolonged alkali therapy actually diminished the incidence of stone formation.

TABLE 4.—*Renal Tubular Functional Abnormality*

Syndrome	Reabsorption			Secretion		
	PO_4	Glucose	Amino Acids	H^+	K^+	Isosthenuria
Vitamin D-resistant rickets	+	0	0	0	0	0
Fanconi syndrome	+	+	+	±	±	±
Renal tubular acidosis	+	0	0	+	±	±
Cystinuria	0	0	+	0	0	0
Renal glycosuria	0	+	0	0	0	0

Interrelationships and Therapeutic Implications

The disorders which have been discussed have certain features in common but vary widely in other respects (Table 4). Except cystinuria and renal glycosuria, all of these conditions are characterized by rickets or osteomalacia, and all demonstrate a defect in phosphate reabsorption, which is apparently the only renal defect present in vitamin D-resistant rickets.

The Fanconi syndrome and renal tubular acidosis actually differ in two major respects only: 1. The former is characterized by abnormalities of glucose and amino acid reabsorption; the latter is not. 2. Nephrocalcinosis and nephrolithiasis occur rarely, if ever, in Fanconi syndrome and are extremely common in renal tubular acidosis. Acidosis, and a presumed abnormality in hydrogen ion secretion, are implicit by definition in renal tubular acidosis but occur very frequently in the Fanconi syndrome. Excessive secretion of potassium and the anticipated clinical sequelae are common in both conditions. It has been stated above that the hyperpotassuria may well represent a secondary effect of the abnormality in hydrogen ion transport.

Cystinuria and vitamin D-resistant rickets resemble each other in the specificity of the renal lesion; they differ markedly in the effect on the patient. A familial incidence has been demonstrated in all of the conditions discussed, but only in cystinuria is it quite firmly established that this is never an acquired lesion. The evidence that such is also the case for vitamin D-resistant rickets is very convincing.

Each condition offers distinct therapeutic opportunities. In families with known vitamin D-resistant rickets bone disease should be completely preventable. The outlook in Fanconi syndrome and renal tubular acidosis is less predictable, but many patients have been maintained in a moderately good state of health for many years, although renal failure eventually supervenes in many instances. The outlook, of course, in cases of acquired lesions is also dependent on the underlying disease, for example, Fanconi syndrome associated with multiple myeloma. A few cases each of the Fanconi syndrome and renal tubular acidosis have been reported in which apparently complete cure has occurred.

Cystinuria would probably be diagnosed with much greater frequency if young subjects with nephrolithiasis, and those with a family history of renal stones, were tested for cystinuria. A high fluid intake in such subjects is reported to be more efficacious in prevention of stone formation than attempts at alkalinization of the urine.

The true relationships of this group of disorders in terms of pathogenesis and etiology are only partially known. Precise definition must await further investigation.

Department of Medicine, University of North Carolina School of Medicine.

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Current and Future Problems in the Management of Renal Failure

JOHN P. MERRILL, M.D., Boston

Of the many problems which face the physician who deals with renal failure, both acute and chronic, it is the purpose of this communication to touch upon only a few. The list is necessarily incomplete, and those which are to be discussed will be dealt with in a summary fashion, in the hope of highlighting them for future discussion rather than truly clarifying the issues involved.

For the purposes of this discussion let me somewhat arbitrarily classify renal failure into two groups. The first group comprises those patients whose renal disease is most strikingly manifested by renal losses, or "wasting." This is usually manifested by inability to conserve sodium (and bicarbonate), water, and occasionally potassium. The second group is characterized by inability to excrete, or "retention." In this case the retention consists of the products of metabolism and ingested food, i. e., potassium phosphates, sulfates, organic acids, "X-factors," and, most important, the hydrogen ion. As a general rule, Group I includes the patients with polyuria and with absent or minimal hypertension and vascular disease. Group II is characterized by urine volumes of less than 1500 cc. per day and frequently by elevation of blood pressure and vascular disease. A special subdivision of the latter group is, of course, acute renal failure and anuria, or marked oliguria. The patients in Group I respond most satisfactorily to therapy, since their need is for replacement rather than removal or restriction.

Certain patients with chronic renal failure "waste" sodium and bicarbonate in their urine. For such persons sodium restriction may result in marked aggravation of renal failure, whereas sodium repletion may result in dramatic improvement. These patients are usually polyuric and without significant hypertension or hypertensive vascular disease. Arbitrary restriction of dietary sodium is one of the commonest errors of treatment of patients with renal disease. A second error arises from the myth that patients with renal failure have a "fixed urinary specific gravity." This has given rise to the belief that if the urinary specific gravity is fixed, i. e., contains the same amount of solute per unit volume, then the larger the volume the more solute should be excreted. This also is false. Patients with renal failure can dilute their urine, except in the most terminal stages. I have shown that patients with moderate renal failure can indeed markedly increase their urine volume as a result of ingested water. However, the marked dilution that occurs results in very little increase in the 24-hour excretion of solute. The facility with which such a water load is delivered into the urine is impaired, however, as contrasted with the normal. Thus, if the water load is administered too rapidly hemodilution and water intoxication may result before the extra fluid is excreted.

On the other hand, patients in Group II with poor urine volumes and with some degree of hypertension frequently are acidotic, not because of sodium and bicarbonate wasting but because of their inability to excrete hydrogen ion. Under such circumstances, the decrease in serum bicarbonate

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which results is respiratory compensation for hydrogen ion retention, which in turn tends to prevent the critical and important change in pH. Treatment of the bicarbonate value alone by the infusion of sodium bicarbonate is treatment of only the result, not the cause, of the difficulty. However, the compensatory mechanism of the bicarbonate-carbonic acid buffer system is not completely effective in its defense of plasma pH. At serum bicarbonate concentrations of approximately 1 mM. per liter it becomes increasingly less effective. Therefore, if the cardiovascular apparatus permits, the use of sodium bicarbonate may be worthwhile when the serum bicarbonate drops below 17 mM. per liter.

The metabolic defect which occurs in patients with renal failure as the result of accumulation of metabolite in the extracellular fluid may be a profound one, and one whose nature is for the present largely unclear. Its effect upon the central nervous system, upon red cell production and survival,[3] and upon the distribution of electrolytes between cellular and extracellular compartment[4] may cause profound disturbances in all these parameters. The recognition of the underlying role in the metabolic defect in production of these abnormalities is critically important, since correction depends upon such an understanding.

I have been able to demonstrate in red cells from uremic patients metabolic lesions which result in impaired transport of sodium and potassium across the membrane. If, as seems probable, this defect obtains in other body cells, it may well explain the hyponatremia and hyperkalemia which occur in chronic renal failure independent of sodium depletion or potassium excess. Under these circumstances a new equilibrium between cells and extracellular fluid has been established for these cations. Attempts to "correct" extracellular concentrations by loading with sodium or depleting of potassium is to treat the result, not the cause, of the lesion.

It is well known that acidosis per se may predispose to elevation of the serum potassium. Thus, inability to excrete hydrogen ion may result in the paradox of an elevated serum potassium in a patient who may actually be potassium depleted. Such a patient with a serum potassium of 5 or 6 mEq. per liter may have as much as 20% or 30% deficit of intracellular potassium. Obviously treatment of such a person by potassium restriction alone may further aggravate the intracellular deficit. This knowledge is particularly important to those who attempt to treat renal failure, either acute or chronic, with the artificial kidney. The use of this apparatus to effect profound and rapid changes in the composition of extracellular fluid must be done only with the knowledge that such changes may not be in keeping with intracellular composition or with the rate at which the organism is capable of compensating for such changes.

With the advent of new, mass-produced, and technically adequate artificial kidneys,[1] the role of this technique in the treatment of acute and chronic renal failure must be reemphasized. It should be stressed again that many cases of acute renal failure can be perfectly adequately handled with conservative therapy.[2] Others, particularly the severely traumatized patients or those with infection, may be so critically ill as the result of a rapid accumulation of protein catabolites and cell break-down that conservative measures alone may not suffice. Here the artificial kidney may play an important and perhaps life-saving role. It must always be used, however, in conjunction with the best methods of conservative management as well as general medical treatment. Acute potassium intoxication is an obvious indication for treatment if it cannot be controlled by other methods. Equally as important is the recognition of the fact that "the uremic syndrome" in acute renal failure may be helped by hemodialysis. Here improvements in the level of awareness may help to prevent pulmonary complications, which are so frequently the cause of death

in these patients. The criteria for the use of dialysis in these instances are clinical ones, and no one blood chemistry or combinations thereof can do anything more than supplement the clinical acumen.

The anemia of uremia has been demonstrated to be due both to decreased erythropoiesis by the bone marrow and to a hemolytic component probably related to the abnormal composition of the extracellular fluid.[5] In some cases the hemolytic element can be improved by correcting this abnormal composition by dialysis.[3] Two major hazards exist in the repeated transfusions that frequently are thought to be necessary in renal failure. One is the development of antibodies to the usually weak antigens of the blood subgroups.[6] These have been repeatedly shown to be the cause of hemolytic transfusion reactions following multiple transfusions. More recently it has been pointed out that isoantibodies to white cells may develop after repeated transfusions and that these are the cause of the pyrogen response seen in such instances.[7] It can be avoided to some extent by the transfusion of fresh packed red cells from which the white cells or buffy coat have been removed. Since, however, cardiac function is not impaired until the normochromic normocytic hematocrit drops roughly below 25 and since some degree of anemia also tends to stimulate the failing bone marrow, transfusion to "normal values" is generally useless and may be dangerous. It has been our practice to maintain the hematocrit somewhere between 25 and 30.

One of the major problems in the management of renal failure both acute and chronic is infection. In our series of 375 patients with acute renal failure over 30% of the deaths were directly attributable to infection. The majority of these occurred after the beginning of the diuretic phase, when one could reasonably expect that kidney function would have continued to improve. Since many of these patients are post-surgical or post-traumatic, wounds are a common portal of entry, and infection has directly been responsible for dehiscence of abdominal wounds in eight of our fatal cases. Bronchopneumonia is another frequent cause of death. In many of our cases the antibiotic-resistant hemolytic Staphylococcus so prevalent in the hospital population has been the major offender. It has been our custom to place such patients on reverse precautions to protect them from the flora of hospital personnel. A further analysis of hospital practice in the sick room, however, has revealed appalling evidence of our lack of proper attention to this problem. The use of the dry mop in the hospital sick room to stir up clouds of dust laden with hemolytic Staphylococcus and the custom of returning blankets each morning to the ward linen shelf to be redistributed the following evening to other patients with their bacterial cargo is to cite only two.

It is now generally recognized that chronic low-grade pyelonephritis is one of the major problems confronting those who deal with renal disease today.[8] The absence of preexisting signs or symptoms suggestive of acute pyelonephritis frequently makes the patient unaware of the existence of this disease until the onset of renal failure or hypertension. There are those, indeed, who feel that chronic pyelonephritis plays a major role in the etiology of much of so-called malignant hypertension.[9] Studies on the etiology and prophylaxis of chronic pyelonephritis must be the subject of intensive research in the future. There is much suggestive evidence at present pointing toward the role of the indiscriminate use of the indwelling catheter as a precipitating factor in chronic pyelonephritis.[10] Investigation of this subject suggests one avenue of approach to the prophylaxis of this disease for which treatment is so frequently disappointing.

In future work in renal disease the immunologist will have a special role. In pyelonephritis itself there is some evidence suggesting that in part the disease may result from an immune reaction to invading micro-organisms. The etiology of glomerulonephritis in the human remains obscure.

Its relation to preceding attacks of so-called nephritogenic streptococci seems to have been established,[11] but the mechanism by which glomerulitis is produced in the human has not been clearly spelled out. Current evidence from animal work suggests that the patient with acute glomerulonephritis may be forming antibodies against his own glomerular tissue.[12] In some fashion glomerular protein has been altered by contact with the product of the hemolytic Streptococcus. This altered protein now constitutes an antigen foreign enough in its composition so that antibodies are formed against it by the patient's own reticuloendothelial system. As yet, however, evidence of circulating antibodies in acute glomerulonephritis has not been evinced in the human. Recently, however, the development of glomerulonephritis in the transplanted kidney in two identical-twin recipients after removal of the patient's own damaged kidneys suggests very strongly that circulating antibodies capable of causing glomerulonephritis do exist in the human.[13]

The treatment of chronic renal failure is usually at best a palliative procedure. Cure of chronic renal disease is rarely possible in the sense that we can replace the nonfunctioning tissue. This, however, would be the ideal therapeutic goal. It has been possible to attain this goal at the present writing by transplanting a normal kidney in eight cases from the healthy identical twin to his sibling with chronic renal failure.[14] This has been proved to be a technically feasible procedure in the human. Unfortunately, it is successful only between identical twins. The reason for the failure of homografted kidney in any species is a challenging problem for the immunologist of the future. Indeed, since the problem appears to be germane to the transplantation of any tissue, it has wider significance than that in the field of renal disease. At the present time it appears that the transplanted kidney fails because it behaves in the recipient as foreign protein to which antibody is formed. This antibody-antigen reaction results in the rejection of the transplanted tissue. Insofar as transplantation rejection in the human is concerned, each person behaves as foreign tissue to any other person (with the exception of identical twins). The homograft problem thus revolves around our efforts to modify either the donor's individual specific antigen or the formation of antibodies against it. The ultimate solution to this problem is elimination of the rejection response without destroying the integrity of either donor or recipient tissue. Several approaches to this problem are currently being employed. It has been possible to inject embryo mice while still in utero with spleen cells from prospective donor strains. At this stage in its development the reticuloendothelial system of the embryo is still too "immature" to recognize as foreign tissue the injected cells. It therefore becomes "acclimated" to the specific donor antigen. Thus, when the animal is born and matures, it will accept skin grafts from the donor strains.[15]

This phenomenon is known as "tolerance," but it has obvious limitations from the clinical standpoint. Two other approaches are under active investigation in this laboratory. It is possible so to destroy the reticuloendothelial system of prospective recipients by lethal doses of x-irradiation that they are no longer capable of producing "antibodies" to foreign tissue. Since such a procedure also destroys hematopoietic tissue, survival is obtained by grafting the animals with bone marrow from the prospective skin donor. The survival of the grafted bone marrow prevents death from agranulocytosis and thrombocytopenia, and, since the recipient animal now has "learned" to tolerate donor strain marrow cells, it will also tolerate skin grafts from the same animal and presumably kidney homografts as well. In our laboratory Dr. Murray and Dr. Porter have produced successful bone marrow "takes" in 38% of rabbits treated in this fashion.[16] Finally, we have become engaged in a study of a soluble antigen derived by ultrasonic disintegration of leukocytes. This soluble antigen appears to have the proper-

ties of the transplantation antigen, although reaction is species-specific rather than individual-specific. By means of a precipitin test my co-workers and I have suggestive evidence for "antibodies" in the plasma of rabbits on whom serial skin homografts have been performed. It is possible that when the chemical structure of such a substance is further delineated and made more specific it might be utilized to insure a successful take of a homograft by either "desensitizing" the recipient or producing "tolerance."

Summary

Some of the current problems in the treatment and evaluation of acute and chronic failure have been discussed and the direction of future research on the general problem of renal disease indicated. It seems probable that when and if the immunologic barrier to successful homografting is reached transplantation of the human kidney may result in a literal "cure" for chronic renal disease.

721 Huntington Ave. (15).

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The Role of Hemodialysis (Artificial Kidney) in Acute Poisoning

GEORGE E. SCHREINER, M.D., Washington, D. C.

The role of the artificial kidney in acute human poisoning may be considered in two distinct categories: (1) *dialyzable poisons*, wherein the rate of removal is critical to the welfare of the patient, and (2) *nephrotoxic poisons*, which produce damage to the kidneys and are not qualitatively different from other causes of acute renal insufficiency. In some instances, general toxicity may be produced from the poison itself, while in others it is a product of the uremic syndrome. It is the purpose of the present study to review eight years of experience with clinical dialyses in acute poisonings and to summarize related studies, with particular emphasis on the role of the artificial kidney in dialyzable poisons.

Dialyzable Poisons

The effective use of hemodialysis in any acute poisoning is based on the following assumptions:

1. That the poison molecule can diffuse through cellophane from plasma water and has a reasonable removal rate, or dialysance.

2. That the poison is sufficiently well distributed in accessible body-fluid compartments. If substantial fractions of the absorbed poison dosage are bound to protein molecules, concentrated in important fluid compartments (e. g., cerebrospinal fluid), or attain a significant intracellular concentration, then effective dialysis will be sharply limited. This restriction is diminished, however, if the "loculated" portion is in diffusion or chemical equilibrium with a significant moiety in the plasma water.

3. That there is a relationship between toxicity and the blood concentration and duration of the body's exposure to this circulating poison.

4. That the amount of poison dialyzed constitutes a significant addition to the normal body mechanisms for dealing with the particular poison under consideration. This should include metabolism, conjugation, and elimination of the substance by bowel and kidney.

It is very apparent that many types of acute poisons are not susceptible to hemodialysis when measured against these pertinent theoretical considerations. Anticholinesterase compounds, as an extreme example, act much too rapidly for a favorable relationship between blood level and clinical toxicity. The same is probably true of the tissue necrosis due to the phosphorus content of rat-paste and matchstick poisoning. It is also apparent that a number of poisons which might fulfill the theoretical criteria listed above have not actually been tried experimentally or clinically. High on our list of "probably" dialyzable poisons would be ethyl alcohol, methyl alcohol,[1] Solox (industrial solvent containing ethyl alcohol and methanol),[2] bile acids, isoniazid,[3] lithium, soluble isotopes, and certain long-acting antibiotics in sensitivity states. This report, however, will not further consider "improbable" or "probable" lists of poisons but will focus on those for which actual removal has been established beyond reasonable doubt by chemical measurement or definite reversal of a clinical state. This list is summarized in Table 1.

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From the Department of Medicine and the Renal Laboratory, Georgetown University School of Medicine.

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TABLE 1.—*Presently Known Dialyzable Poisons*

Phenobarbital
Barbital
Secobarbital
Amobarbital
Pentobarbital
Diphenylhydantoin
Acetylsalicylate
Methyl salicylate
Bromide
Potassium thiocyanate
Ammonia
Sodium chlorate
Strontium and radiocalcium
Tritium
Glutethimide

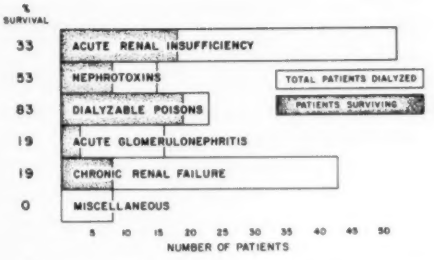

Fig. 1.—Eight years' experience with hemodialysis; distribution of etiology and survival; 160 patients, 242 dialyses.

The Renal Laboratory at Georgetown University Hospital has been particularly interested in this subject, since the first patient with acetylsalicylic acid poisoning was dialyzed in September, 1950.[4] Our total experience is summarized in Table 2. There have been 27 dialyses in 24 patients, who represent 14% of our total of 168 patients dialyzed up to April, 1958. The survival rate in this group is 83%, appreciably higher than the survival rate of 37% in our entire series of 258 dialyses in 168 patients and higher than any other etiologic category (Fig. 1). The four deaths in the series of dialyzable poisons are not difficult to account for. One was due to a cerebral hemorrhage in an elderly patient with barbiturate poisoning who had only a unilateral return from flaccid coma. One patient with salicylate poisoning died from irreversible brain damage, but dialysis was terminated after only one hour because of technical difficulties. One patient with salicylism died from irreversible liver necrosis because she was referred long after the ingestion of a massive amount of salicylate. One patient had ingested an unknown poison, did not respond to the dialysis at all, and probably does not belong in the group of dialyzable poisons but is included in the series for the sake of completeness.

TABLE 2.—*Hemodialysis in Acute Poisoning, January, 1950, to April, 1958*

	Patients, No.	%
Total patients dialyzed	168	100
Surviving	62	37
Patients with dialyzable poisons	24	14
Surviving	20	83
Barbiturate	15	
Acetylsalicylate	4	
Glutethimide	2	
Bromide	1	
Diphenylhydantoin	1	
Methyl salicylate	1	
Patients with nephrotoxins	15	9
Surviving	7	47
Bichloride of mercury	8	
Carbon tetrachloride	5	
Mercuric cyanide	1	
Sulfonamide	1	

Barbiturate Poisoning

The moderately high suicide rate in the United States * is expressed in some geographic areas by a fashion for the overingestion of barbiturates. This is aided by the availability of this agent in many communities without strict regulation by the pharmacy profession. We estimate that more than 15000 patients are hospitalized each year for barbiturate poisoning. The admission rate at Georgetown Hospital has exceeded one per month.

Although it has long been theorized that the most physiologic approach to any poison is the direct removal of it, the study of Kyle et al.[6] from this laboratory was the first known clinical application of hemodialysis to the problem of barbiturate intoxica-

* In 1954, suicide mortality in the American white population was 10.8/100,000 population, as compared with 2.0/100,000 in Ireland and 23.4/100,000 in Japan. Suicide is the second commonest cause of death among college students, accounting for 8% to 12% of deaths in this group.[5]

TABLE 3.—*Treatment of Acute Pentobarbital Poisoning by Resin Column and Hemodialysis*

Date	Time	Source	Conditions	Barbiturate Level, Mg/100 Ml.
4-23-57	11:00 p. m.	Venous		4.7
4-24-57	2:00 p. m.	Venous	After fluids	4.6
	8:00 p. m.	Arterial	Before resin Column I	6.0
	8:30 p. m.	Arterial	After 15 min of resin	5.2
		Venous	Outflow of resin column	4.9
	9:00 p. m.	Arterial	Before resin Column II	5.0
	9:30 p. m.	Arterial	After 15 min. of resin	5.0
		Venous	Outflow of resin column	3.0
4-25-57	3:30 a. m.	Arterial	After 5 hr. hemodialysis	3.6
	9:00 a. m.	Venous	Follow-up	2.9
	9:00 p. m.	Venous	Follow-up	1.7
4-26-57	9:00 a. m.	Venous	Follow-up	1.1
4-27-57	9:00 a. m.	Venous	Follow-up	0.3

tion. Two patients with pentobarbital (Nembutal) and amobarbital (Amytal) poisoning were successfully treated. We have subsequently reported eight additional cases, together with an undialyzed series and related studies.[7] Since then, five more patients have been dialyzed, including three on the twin-coil artificial kidney. In this eight year total of 18 dialyses on 15 patients, there has been only one death (cerebral vascular accident). Data on the unpublished cases are detailed in the appended case histories (Cases 1-5). The blood barbiturate levels in response to therapy of Case 3 (RD-174) are listed in Table 3. The patient's blood was first circulated through a lactate-loaded anion-exchange resin column. Later, conventional hemodialysis was employed. Figure 2 depicts the clinical and chemical results of dialysis in Case 4 (TC-36). Experience with barbiturate dialysis has also been reported by others.[8-11]

The indications for hemodialysis in barbiturate poisoning are as follows:

1. Progressive deepening of anesthesia or deterioration of the clinical state (severe hypopnea, areflexia, shock, cyanosis).

2. Known ingestion of a potentially fatal dose with the probabilities of more or less complete absorption from the gastrointestinal tract (e. g., 3.0 gm. for short-acting barbiturates and 5.0 gm. for the long-acting variety).

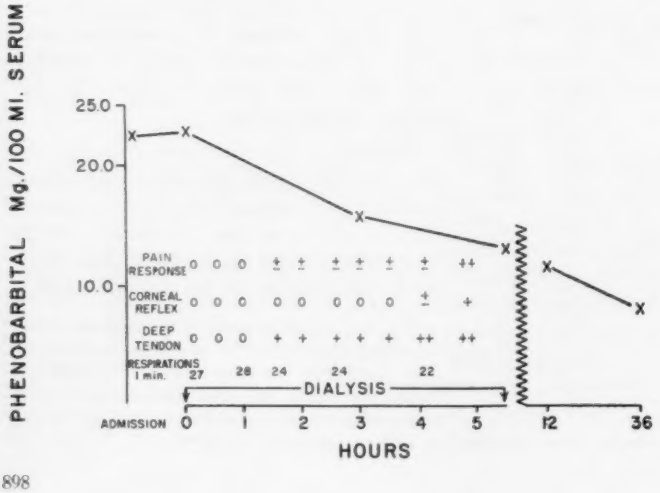

Fig. 2 (Case 4).—Clinical dialysis of phenobarbital, July 25, 1957. Change in the barbiturate blood level during dialysis of a 59-year-old white woman who ingested an unknown amount of sedatives. Note the concomitant improvement in pain response and reflexes.

3. A blood barbiturate level[12] in the potentially fatal range (e. g., 3.5 mg/100 ml. for short-acting and 8 mg/100 ml. for long-acting drugs).

4. The development of a severe complication (e. g., hyperpyrexia or aspiration pneumonia) or coexistence of a medical condition increasing the hazards of prolonged coma.

Since contamination with a small amount of phenobarbital can disproportionately raise the blood level, it is necessary to get the maximum amount of specific information from patient, family, druggist, referring physician, or policeman. Searching bedroom, bathroom, or apartment will usually yield the medicine bottle needed for precise information. When such historical data are scanty, it is possible chemically to approach the identification of the drug by comparing the ultraviolet absorption spectrum of the unknown serum with the family of absorption curves produced by standard preparations of the commonly used barbiturates (illustrated in Fig. 3). Application of this method to a clinical problem is shown in Case 6. In any doubtful situation experienced clinical judgment must prevail over laboratory data.

Since any dialysis depends on the blood-to-bath concentration gradient, the artificial kidney is most dramatic in the patients poisoned with long-acting drugs such as barbital and phenobarbital. It is possible to obtain in the bath up to 40% of the known ingested dose. In short-acting barbiturate poisoning, the rate of drug removal is much slower and recovery of more than 20% of the ingested dose is not usual. However, a significant metabolism of the drug takes place during the six to eight hours of the procedure which may be the critical hours for survival, particularly in the complicated patient. In exceptionally severe cases of the short-acting type, it may be desirable to continue dialysis longer than the conventional six-hour period.

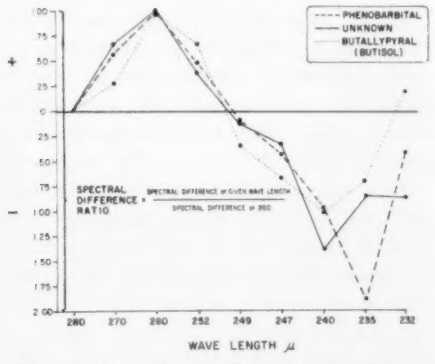

Fig. 3.—Use of the absorption spectrum to identify specific barbiturates.

Mobilization of drugs from substances other than blood can be demonstrated by the recovery in the bath of more barbiturate than can be accounted for by the product of circulating volume and the Δ serum concentration. Mobilization from tissue probably occurs, and the occasional rapidity of clinical response implies potential mobilization from the brain. Reactivation of an inert narcotized intestinal tract has been noted several times in our experience and may produce a secondary peak in blood level exceeding the initial concentration. This is demonstrated in Figure 4, which depicts the serum levels in a 28-year-old woman who ingested 25 gm. of phenobarbital, which represented a dose of 664 mg/kg., or many times the LD_{99} for this drug in animals. Absent borborygmi were noted before the first dialysis. Peristalsis restored as a result of the first dialysis reinstituted intestinal absorption, and a second peak in blood level resulted with a return to deep coma.

Reduced arterial hemoglobin has been noted in several cases through the plastic arterial cannula, and occasional instances of sudden clinical improvement after the start of dialysis are probably ascribable to the oxygenating capacity of the artificial kidney, which is thus capable of adding to the cardiac output 200 to 300 ml. per minute of warm oxygenated blood.

It may be noteworthy that only two patients in our dialysis series have been known to make another suicide attempt. One was a gesture with a small amount of barbiturates, the other ended in a fatality by another means. Many patients, including the case illustrated in Figure 4, have effected apparently complete rehabilitation.

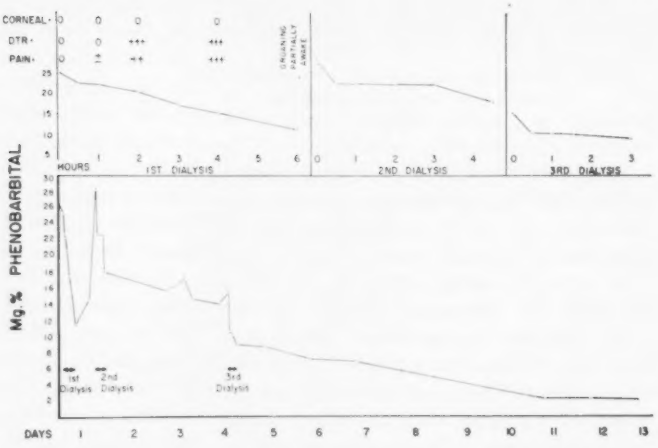

Fig. 4. — Phenobarbital intoxication in 26-year-old white woman who ingested 250 0.1 gm. tablets of phenobarbital; total dose 25 gm. Body weight 83 lb.

We may conclude, therefore, that the artificial kidney can remove significant amounts of barbiturate from the body, can result in directly observable reversal of the anesthetic state, can shorten the period of coma and deep sleep, and can lower the incidence of complications by restoring cough and other reflexes. In the unusual cases of massive ingestion it may offer the only chance for survival.

Salicylate Poisoning

Salicylates are quantitatively the most important medical chemical produced. Acetylsalicylic acid production in 1955 amounted to 658,000 lb. per month and shows annual increases of over 10% per year. Salicylates account for more than 4% of all fatal poisoning in the United States [13] and were found to account for 14% of 834 deaths from accidental poisoning in children under the age of 5 years.[14] In children, the commonest forms are accidental ingestion of flavored tablets, swallowing of adult tablets or liquids out of curiosity or "oral" factors,[15] and ingestion of methyl salicylate as wintergreen oil. Because of its accessibility, acetylsalicylic acid is sometimes chosen by adults as an instrument of suicide, but its irritative effect on the gastric mucosa generally produces vomiting and lessens the incidence of truly severe poisoning.

Salicylate was among the first chemicals dialyzed from animals by Abel, Rountree, and Turner [16] in 1913. The first attempt at clinical dialysis of salicylate was reported from this laboratory [4] in 1951, and the first successful dialysis was carried out in 1954.[17] We have recently reviewed the chemical, pathologic, and clinical considerations in applying hemodialysis to acute salicylism.[17] Because of the wide range of tolerance, one cannot predict survival or death accurately from the estimated dose or the blood concentration,[18] but, in general, the ingestion of more than 20 gm. of acetylsalicylic acid or blood salicylate levels over 50 mg/100 ml. are often associated with severe toxicity. Experienced clinical judgment is necessary to select patients for dialysis. Case 7 illustrates the type of patient who can usually be managed without dialysis. However, patients exhibiting central nervous system signs, severe depression of prothrombin time, or coma should be seriously considered for the artificial kidney. Our experience with a patient with irreversible brain damage,[4] (RD-6) who had a salicylate blood level of 55 mg/100 ml., and the observation of irreversible liver necrosis in Case 8 (RD-105) with a salicylate level of 115 mg/100 ml., suggest that earlier use of dialysis in patients with high blood levels may reduce the severity of subsequent pathology.

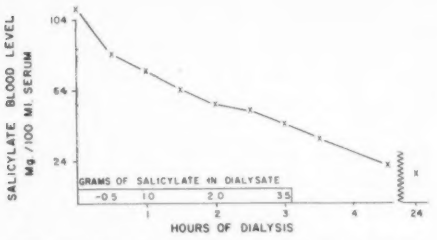

Fig. 5 (Case 9).—Sept. 29, 1956, rapid dialysis of salicylate from a 21-month-old semicomatose infant with ingestion of approximately 30 ml. of methylsalicylate.

To date we have dialyzed four patients with acetylsalicylic acid poisoning and one with methyl salicylism. The latter patient, Case 9 (RD-160) was 21 months old and the youngest patient in our dialysis series. His initial blood level of 110 mg/100 ml. was reduced to 29 mg/100 ml., as shown in Figure 5, and we feel that early dialysis was probably life-saving in this instance. To our knowledge, this is the first reported instance of the successful use of hemodialysis in methyl salicylate poisoning.

Details of salicylate dialysis in Case 10 (TC-52) are presented graphically in Figure 6, and illustrative case histories are appended.

We conclude that the artificial kidney can remove salicylates 20 or more times faster than healthy kidneys working optimally and that early application in the "silent period" when blood salicylate levels are high may prevent the development of serious or fatal brain and liver damage. Two deaths in our dialysis series and one death on admission before dialysis should serve to emphasize the serious nature of salicylate poisoning and the need to regard it as a true medical emergency.

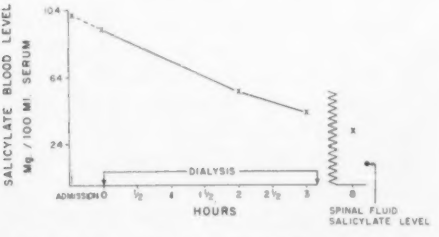

Fig. 6 (Case 10).—Oct. 21, 1957, change in the blood salicylate concentration during dialysis of a patient with overdose of acetylsalicylic acid tablets.

Bromism

The relatively small atomic size, extracellular distribution, and high plasma concentration of bromide in chronic clinical bromide poisoning have been cited as reasons for considering bromide as the ideal dialyzable toxin. In the first reported case, Merrill and Weller [19] dialyzed a woman with 23 mEq. of bromide per liter in the serum and recovered 166 mEq. in the dialyzing solution. In December, 1956, we dialyzed a

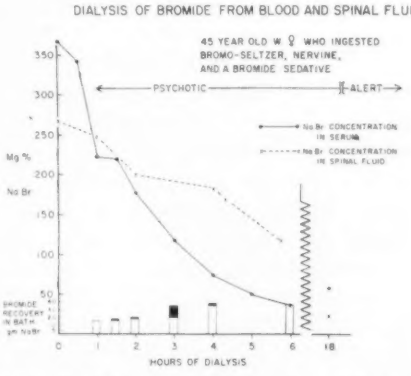

Fig. 7.—Dialysis of bromide from blood and spinal fluid of a 45-year-old white woman who ingested Bromo-Seltzer, Nervine, and a bromide sedative.

46-year-old woman with acute and chronic bromide intoxication who had a blood level of 43 mEq. per liter and a spinal fluid level of 33 mEq. of sodium bromide per liter when first measured. Removal of 370 mEq. of sodium bromide in the dialysate was accomplished during a time interval when 1.5 mEq. was excreted in the urine. Physiologic data on this case have been reported in abstract form,[20] and the details of her psychiatric changes have been separately reported.[21] Further information is presented here in the detailed case report, Case 11 (TC-4). The changes in serum level, cerebrospinal fluid level, and the cumulative bath recovery of sodium bromide are pre-

sented graphically in Figure 7. The dialysance of bromide calculated by Wolf's [22] formula was 124 ml. per minute at a blood flow of 230 ml. per minute. This is comparable to the dialysance of urea. Successful dialysis in bromide poisoning has also been reported by Anthonisen et al.[23]

We conclude that hemodialysis is the most rapid and effective method yet devised for the treatment of severe bromide intoxication and markedly shortens hospitalization. The half-life of sodium bromide level under other forms of therapy is 9 to 27 days. Delayed reequilibration across the blood-brain barrier may account for delay in the response of the clinical picture to dialysis.

Glutethimide (Doriden)

Glutethimide (2-ethyl-2-phenylglutarimide) is a widely used proprietary hypnotic and sedative. It is poorly soluble in water, may have irregular gastric absorption, and has an internal recirculation via biliary secretion and absorption which may result in prolonged toxicity with cyclic changes in the clinical state of the patient. We have very recently published an extensive review of this subject.[24] Clinical and pharmacologic details and bibliography will not be repeated here. We have seen eight cases of acute poisoning with this drug. Successful dialysis was carried out in two patients, one in our laboratory, and one at the Walter Reed Army Medical Center. There has been one death in a patient who, in retrospect, should have been dialyzed. Blood glutethimide levels are low, and the kinetics of distribution and dialysance have not been worked out. It seems probable that in severe glutethimide poisoning it may be desirable to continue hemodialysis for more than the customary six hours or to interrupt shorter periods of dialysis with an equilibration period.

We conclude that glutethimide is dialyzable and that the artificial kidney is a useful adjunct in the management of severe cases.

Diphenylhydantoin (Dilantin)

Diphenylhydantoin is a widely used water-soluble anticonvulsant, which is freely prescribed in large amounts in the treatment of epilepsy and is, therefore, readily available. Severe toxicity may occur from accidental (automatism) or suicidal ingestion. Nausea and vomiting, irritability, vertigo, headache, ataxia, and even death have been reported from large doses.[25,26] We have previously reported [7] (Case 9) a case of combined diphenylhydantoin and phenobarbital poisoning treated by hemodialysis. At that time, we investigated diphenylhydantoin and found that it did not produce a high chemical blank and did not interfere with barbiturate determinations. More recently, we dialyzed a 2-year-old boy who was one of 11 children with acute diphenylhydantoin poisoning. Details of the case history are presented in Case 12 (TC-38).

Miscellaneous Poisoning and Toxic States

Kiley [27,28] and co-workers have clearly demonstrated that ammonia can be removed directly from the blood by hemodialysis and have reported a dialysance of 50-80 ml. per minute at a blood flow of 100 ml. per minute. Several patients have been reported where the ammonia level was implicated in the mechanism of hepatic coma. Ammonia removal has improved some cases of hepatic coma,[29] and ammonia may rarely be implicated in uremic coma.[30] We have documented reversal in minutes from a nine-hour areflexic coma in a man with ureterosigmoid anastomosis and a uremic syndrome.

Danzig and Kringel [31] have reported the successful treatment of thiocyanate psychosis by hemodialysis with removal of 3.1 gm. and reduction in thiocyanate blood level from 24.8 to 1.5 mg/100 ml.

Kiley, Barenberg, and Conklin [32] have studied the removal of tritium by the artificial kidney and suggest its use in accidental overdosage. They report a dialysance of 185 ml. per minute in excess of a concomitant urea dialysance.

Looney, et al.[33] have recently reported the successful use of dialysis and ion-exchange resin columns for the removal of radiocalcium and strontium from the body. They removed 41% of ingested radiocalcium from a dog during a six-hour dialysis, while concomitantly removing 1% of the total skeletal calcium. This has obvious implications in the toxicology of heavy isotopes.

MacNeill[34] and co-workers have commented on the use of dialysis and exchange transfusion in a case of sodium chlorate poisoning.

Incidental Observations

A number of incidental observations have been made in the course of treating this interesting group of patients and may warrant brief mention here.

Hypocalcemia, often of severe proportions, was accidentally discovered while chemical studies on barbiturate poisoning were being done and has become the subject of a separate study and preliminary report by Canary et al.[35]

Unlike uremic patients who have elevation of many serum metabolites, most poison victims have normal concentrations of the common chemical parameters. Dialysis may wash them out to low values which are unique in biologic material. For example, postdialysis serum inorganic phosphorus concentrations in a series of poison patients were 0.5, 3.1, 0.5, 0.8, 1.6, 0.4, 0.7, 1.9, 0.4, 0.9, 1.4, and 0.7 mg/100 ml. We could attribute no adverse effects to these remarkably low concentrations. Similarly, postdialysis uric acid concentrations were 1.0, 3.7, 2.2, 2.7, 3.3, 1.5, 1.3, 2.7, 2.2, and 1.3 mg/100 ml. It should be cautioned that hemolysis late in dialysis was seen in one case in this series and has been reported verbally to us by other investigators. This could conceivably be related to the washing out of some extracellular solute.

Hyperpyrexia has been a prominent problem with central nervous system damage, and in these cases the artificial kidney bath temperature could be lowered to act as a cooling device.

Since most of these patients have normal red cell volumes, in cases of extreme emergency where priming blood is not available, it is possible to start dialysis by priming the machine with 5% albumin in saline or physiological dextran. We have also used mixtures of blood and albumin in such situations.

Many antibiotics, such as penicillin and chloramphenicol, are dialyzable. In patients with aspiration bronchopneumonia it is necessary to restore antibiotic concentrations after dialysis.

Lastly, dialysis is not a substitute for a good airway.

Nephrotoxic Poisons

The use of hemodialysis in acute nephrotoxic poisoning has, up to the present, been based on the thesis that nephrotoxins are just another form of acute renal insufficiency. Indications for dialysis have, therefore, been indistinguishable from those in acute tubular necrosis and have included (1) intractable hyperkalemia, (2) fulminating uremic syndrome, and (3) prolonged course.

To date we have dialyzed 15 patients with nephrotoxic injury due to bichloride of mercury, mercuric cyanide, carbon tetrachloride, and sulfonamides. These represent 9% of our total patients dialyzed. Seven patients recovered, for a survival rate of 47%. This group is compared with others in Figure 1 and Table 2.

A detailed analysis of these patients is the subject of another study[36] and will be considered beyond the scope of this report. It should be remembered, however, that time-cytotoxic relationships may exist for many of these compounds and that removal from the blood stream may prevent some of the now accepted pathology. We have[37] preliminary experimental and clinical data to indicate the feasibility of removing mercury from the anuric patient. Perhaps similar means can be found for other nephrotoxins.

Comment

Acute accidental and intentional poisoning, once relegated to the domain of industrial medicine, is now recognized as endemic to the household. Clinical surveys, large [14] and small,[38] have been impressive by the prevalence of this problem, and every physician is aware of its inherent tragedy. Short of total prevention, which would require a psychiatric millenium, there has been a large void in the therapeutic aspects of human toxicology. The age of specific antidotes and quantitative metabolic antagonists is, unfortunately, not yet with us for many of the common severe poisons. Treatment has, therefore, been symptomatic and supportive.

We believe that the present study embracing 24 patients with dialyzable poisons and 15 patients with nephrotoxic injury should be reasonably convincing of the value of hemodialysis in this situation. The long list of known dialyzable poisons (Table 1) should grow before this paper is published. With accumulation of more experimental and clinical data, it may be possible to invade the "silent period" of more and more poisons and to remove them before any clinical picture develops. This will require considerable education and the refinement and availability of chemical techniques for the fast-growing number of medications that the flesh is heir to. Even at the present state of our knowledge it would seem that an experienced team with an artificial-kidney installation (Fig. 8) would be a valuable addition to any poison center.

Summary

The role of hemodialysis in the study and treatment of acute poisoning is assayed from eight years' experience embracing 24 patients with dialyzable poisons and 15 patients with nephrotoxic injury. Survival rates were 83% and 47%.

The principles for the selection of poisons are discussed. They include (*a*) diffusibility, (*b*) distribution in equilibrium with plasma water, (*c*) a time-dose-cytotoxic relationship, and (*d*) a dialysance significantly additive to metabolism and excretion.

Barbiturate, salicylate, bromide, glutethimide (2-ethyl-2-phenylglutarimide [Doriden]), and diphenylhydantoin (Dilantin) poisoning are reviewed in detail, with illustrative case histories appended.

The first known instance of successful dialysis of severe methyl salicylate poisoning is presented, with reduction in blood salicylate level from 110 to 29 mg/100 ml.

Fig. 8.—The twin-coil artificial kidney in use at Georgetown University.

Early dialysis is suggested to abort the full clinical picture in dialyzable poisons and nephrotoxic injury.

Case Histories

Acute Barbiturate Poisoning

CASE 1 (RD-115).—A 46-year-old white married woman was admitted in deep coma at 5 p. m. in October, 1955. She was last seen awake at 8 a. m. and was found at 3 p. m. in bed in deep coma. She was believed to have taken about 8 pills of 3 grains amobarbital (Amytal) sodium and 12 or more tablets containing equal parts of secobarbital and amobarbital sodium (Tuinal). Chlorpromazine was also available to her. Emergency therapy was given by her physician, who noted mild cyanosis and a blood pressure of 110/60. There was a past history of melancholia treated by a psychiatrist.

On physical examination here, the blood pressure was 80/60; pulse, 80, and respirations, 24. The patient was in coma, with stertorous breathing and flaccid tongue. Pupils were constricted and barely reacted to light; corneal and deep-tendon reflexes were absent. There was no response to painful stimuli. The swallowing reflex was present but weak. An airway was established; oxygen and fluids were begun, but in a half-hour the respirations became very shallow and the blood pressure began to fall. She was treated with picrotoxin which improved only the blood pressure, and a decision was made for dialysis. The blood barbiturate level on admission was 7.7 mg. %. Later in the afternoon it was 5.7 mg. %, and blood taken from the arterial cannula at start of dialysis was 5.3 mg. %. It had the spectral difference (Fig. 3) of a short-acting barbiturate. Dialysis was begun at 7 p. m., with pupils dilated and corneals absent. At the end of one and one-half hours the corneal reflexes returned and the pupils reacted to light. Some deep-tendon reflexes were obtained, but the ankle jerk remained absent. Response to painful stimuli was very slow, and levarterenol (Levophed) was still required. At two and one-half hours the barbiturate concentration was 4.2 mg. %., her fingers were cold and cyanotic, and levarterenol was still required. Deep-tendon reflexes were 2+, but the corneals were lost again. There was a poor response to painful stimuli, and the extremities were slightly stiff. At four hours the rectal temperature rose to 103.6 F, and at five hours the patient's blood pressure was maintained for the first time without levarterenol. The plantar withdrawal reflex appeared for the first time, but the patient remained quite flaccid. At five and one-half hours she began to respond to painful stimuli. Deep-tendon reflexes were 2+; the pupils began to react, and the blood level was 3.6 mg. %. The patient was responding well to painful stimuli; the blood pressure was stable, and she was making swallowing movements. A slight hemolysis was noted in the hematocrit supernatant, and hemoglobin was present in the urine. The patient was returned to her room in good condition but had a tendency toward hypotension which required additional amounts of levarterenol. The following morning the endotracheal tube was maintained, and the patient became progressively more alert. Upon awakening, the patient acknowledged taking eight 3 grain (0.19 gm.) amobarbital sodium tablets and twelve capsules containing equal parts of secobarbital and amobarbital sodium and also having been on chlorpromazine (Thorazine), three tablets a day, up until the week before admission. The acknowledged dose of 39 grains (2.5 gm.) of short-acting barbiturates fits well with our estimate of 2.5 to 3 gm. calculated from blood level, estimated body water, and biologic half-life of short-acting barbiturates. The recovery of sodium amytal from the bath amounted to 280 mg. from the first bath, 240 mg. from the second bath, and 267 mg. from the third bath, for a total of 787 mg. The patient made a good recovery and was discharged for psychiatric care.

She was readmitted in May, 1956, for acute barbiturate poisoning of a mild degree, which required no specific therapy, and she was readmitted in May, 1957, for moderately severe drug intoxication which was believed to be due to meprobamate (Miltown). Her progress at this time was satisfactory, and she made an uneventful recovery.

Comment.—We conclude that this patient had a severe case of acute barbiturate poisoning due to combined secobarbital and amobarbital, with a high blood level and a deteriorating state in which hypotension was particularly prominent. It is possible that the combination with chlorpromazine may make the blood pressure worse. It was felt that hemodialysis substantially contributed to her survival.

CASE 2 (RD-148).—A 35-year-old man was admitted to Georgetown University Hospital in July, 1956 while he was on leave from a mental hospital. He was found comatose on the day of admission and was alleged to have taken 88 capsules of secobarbital (Seconal) containing ¾ grain (0.05 gm.) each. He was admitted to another hospital and treated with 4 gm. picrotoxin and intravenous fluids. Serum taken at that time was later determined to have a barbiturate level of 2.4 mg. %, predominantly secobarbital. He was transferred eight hours after ingestion, at which time a second blood level was 3.0 mg. %. Because of the deteriorating clinical state and the rising serum level, he was dialyzed; he had a good clinical response

during dialysis, but later some cyanosis was noted requiring bronchoscopy and suction. The next day he lapsed into a deeper coma, and blood levels 12 and 24 hours after dialysis were 2.5 mg. % and 2.2 mg. %. Thirty-six hours later the secobarbital level was 1.9 mg. %, and the patient was markedly improved and fully reactive. The only physical findings were areflexia during coma, decreased respiratory excursion, and loud rales throughout both lung fields.

Comment.—This case illustrates how a short-acting barbiturate can be a very long-acting barbiturate when taken in high doses. It took this patient 72 hours to become fully reactive, and he could not be ambulated until 96 hours from the time of ingestion. There was a good transient response during dialysis, but the high blood level on the following days suggested that additional amounts of the drugs were being supplied from a reservoir, probably in the small intestine.

Case 3 (RD-174).—A 37-year-old white woman was admitted in April, 1957, eight to twelve hours after the ingestion of an estimated 24 capsules of 1½ grains (0.1 gm.) pentobarbital (Nembutal) and an indefinite quantity of chlorpromazine tablets. She was suffering from a chronic depression. She was seen in the emergency room approximately nine hours from ingestion. The blood pressure was 80/60; respirations, 21; the patient was in profound coma, areflexic, and without bowel sounds. She was seen in consultation about 12 hours postingestion, at which time deep-tendon reflexes were faintly present. Respirations were deep and regular at 20 per minute; blood pressure was stable at 80 to 90/60. The pulse was 100 to 110; ileus was present, but a few local peristaltic movements were beginning to appear. The blood barbiturate level taken at this time was 4.7 mg. %, and the ultraviolet absorption spectrum revealed only pentobarbital. She was treated conservatively with an airway, suction, and at the end of 24 hours there was still a faint ankle jerk. A dusky cyanosis appeared in lips and finger tips. Some progressive deepening of coma and worsening of respiration occurred, and the blood level of pentobarbital at this time remained at 4.5 mg. %. Because of this, it was felt that removal of the drug should be attempted at about 28 hours after admission. At this time an artery and a vein were cannulated, and the patient's blood was passed through a lactate-loaded anion-exchange resin column for two 15-minute periods, producing only a minimal appearance of the knee jerk and some slight improvement in the breathing. There was no improvement in blood pressure or oxygenation, and the patient's clinical state suggested the need for further therapy. She was, therefore, attached to the rotating-drum artificial kidney 30 hours after ingestion. Her reflexes dramatically improved after the two hours of dialysis, and by the fourth hour spontaneous movement was noted. Dialysis was carried out for a total of five hours. The patient showed progressive improvement and was discharged on the eighth hospital day. Data have been summarized in Table 3.

Comment.—This patient, although poisoned with a short-acting barbiturate, remained in coma for more than 24 hours, at which time there was progressive deepening and worsening of her clinical picture. Part of this may have been due to aspiration and an early bronchopneumonia, with some impairment in oxygen exchange that was apparently at a peripheral level and did not respond to intubation and suction. However, the maintenance of a high blood pentobarbital level during this period suggested a considerable tissue or intestinal reservoir. Exposure to anion-exchange resin for investigative purposes did not result in the removal of significant amounts of the pentobarbital. Dialysis, however, markedly improved her clinical picture, with prompt restoration of cough reflexes, which minimized complications of her pneumonia and enabled a rapid recovery.

Case 4 (TC-36).—A 59-year-old housewife was transferred to Georgetown University Hospital with a history of coma of two days following the ingestion of unknown amounts of barbiturates and other substances. Among the probable tablets swallowed were acetylsalicylic acid, phenobarbital, a proprietary preparation of sulfa and phenobarbital, meprobamate (Equanil), and chloral hydrate. She developed an aspiration pneumonia on the first day, necessitating bronchoscopy and tracheotomy. She was treated with gastric lavage, picrotoxin, caffeine and sodium benzoate, clysis, antibiotics, and digitalis because of auricular fibrillation.

There was a past history of a despondent state after her husband had major surgery during the previous year and a reactive depression when she was informed of the presence of carcinoma.

Physical examination revealed a comatose middle-aged woman with a blood pressure of 119/90, pulse 120, respiration 28 and shallow. There were rales in the right lung field, no response to painful stimuli, absent superficial and deep-tendon reflexes, absent corneal reflexes, and miotic pupils with

slight reaction to light. The blood barbiturate level was 22.5 mg. %. The patient was dialyzed on the night of admission, and the postdialysis barbiturate level was 13.2 mg. %. Deep-tendon reflexes and response to painful stimuli returned during dialysis and the corneal reflex later. Data are summarized in Figure 2. After return to her room, the patient remained drowsy but was able to open eyes on command. The last barbiturate blood level was done on the third day after admission and was 8 mg. %. Return from sleep was extremely gradual in this patient, and she could not be ambulated until the sixth or seventh hospital day. Her course was complicated by fever of 12 days' duration due to extensive bilateral bronchopneumonia.

She was discharged on the 17th hospital day.

Comment.—This is a patient with severe phenobarbital intoxication complicated by a number of other drugs which produced marked prolongation of her sleep. The initial barbiturate level was in the distinctly fatal range, and the patient had already developed a rather widespread bronchopneumonia. It was felt that lightening of this coma by the removal of a significant amount of barbiturates contributed greatly to her recovery.

CASE 5 (TC-71, 72).—A 45-year-old white housewife was admitted to Georgetown Hospital in March, 1958. She was known to have severe chronic ulcerative colitis, mental depression, and insomnia and had been admitted to another hospital on an emergency basis for ingestion of sleeping pills. About eight hours previously the patient had been found unresponsive on the floor with the following empty bottles nearby: (1) phenobarbital, 16 mg. tablets, (2) methscopalamine (Pamine) with phenobarbital, (3) pentobarbital, 50 mg. tablets, and (4) green sleeping pills believed to be amobarbital sodium. The exact quantity of drugs taken could not be determined. On her admission to the other hospital the pulse was weak; the blood pressure was 70/0; the respirations, 14, and the pupils did not react to light. Deep-tendon reflexes were absent, and there was no response to painful stimuli. She was treated with 45 cc. of pentylenetetrazole (Metrazol) and nikethamide (Coramine), caffeine, mephentermine (Wyamine), oxygen, penicillin, and intravenous fluids. Gastric lavage was attempted but had to be discontinued because of marked respiratory distress. She was transferred for dialysis.

Upon arrival here the patient was in deep coma. The blood pressure was 110/80; the pulse, 100, and the respirations, 26. Pupils were fixed at 2 mm. and nonreactive to light. Sclerae were injected. There was no gag, corneal, or cough reflex. There was no plantar withdrawal. Deep-tendon reflexes were absent, but there was an unsustained ankle clonus from the right side. Two blood barbiturate determinations spanning a short period of time were 15.3 and 16.3 mg/100 ml., respectively, with the absorption spectrum indicating predominantly phenobarbital. Dialysis was started immediately and was continued for seven hours on a twin-coil artificial kidney with excellent flow rates. At two hours the blood level was still 15 mg. %. The barbiturate concentration in gastric wash fluid was 21.5 mg. % just preceding her dialysis, suggesting continued absorption. During the sixth to seventh hour of dialysis, the patient began to respond to the spoken word and painful stimuli and some reflexes returned, although she remained disoriented. The blood barbiturate level post dialysis was 8.7 mg. %. During the 30 hours post dialysis, the patient developed signs of a complicating pneumonia and had a deterioration in the level of her alertness, and about 30 hours after the first dialysis, she was again in coma with response only to deep pain. A barbiturate level done at this time showed a secondary rise to 10.7 mg. %, which we attributed to further absorption from a bolus in the gastrointestinal tract. Because of this, it was decided to attempt a second dialysis, which was accordingly carried out, with a flow rate of 300 ml. per minute. By the second hour, the patient responded to her name, and a blood barbiturate level after three hours of dialysis was 7.9 mg. %. She became quite responsive, and the dialysis was discontinued after four hours. She remained responsive and made an uneventful recovery and was discharged for psychiatric care on the 14th hospital day.

CASE 6.—A 19-year-old student was admitted to Georgetown University Hospital in June 1958, with a history of having been semicomatose for 10 hours. He had last been seen 14 hours previous to his admission, when he appeared depressed and shortly thereafter was noted to fall asleep. Eight hours before admission, he appeared disoriented, thrashing, and in a hyperactive state and some type of poisoning was suspected. He was known to have access to tablets containing methamphetamine hydrochloride and phenobarbital (Ambar Extentabs) and other medications. At two and one-half hours before admission, he appeared to have cyclic semicoma and maniacal episodes. He was seen by a doctor at this time who noted extremely dilated pupils. Vomiting occurred in the active state.

On admission here the patient was deeply comatose and unresponsive to command or pressure. Temperature was 98.8 F; blood pressure, 130/60; pulse, 110, and respirations, 24. Pupils

were widely dilated but still reacted to light. Corneal reflex was faint; the abdominal superficial reflexes were minimal; ankle clonus was present and sustained for short bursts; there was no plantar reflex and no discernible deep-tendon reflexes. It was felt desirable to attempt to verify the ingestion, and serum was drawn on admission for barbiturate level. The total concentration was 6.9 mg. %, a figure which would be encouraging if the material were phenobarbital or alarming if it were a short-acting barbiturate. An absorption spectrum was carried out, and spectral differences [12] were calculated as graphically represented in Figure 3. The absorption spectrum was most compatible for phenobarbital, which supported the history. On the basis of this, conservative treatment was elected; the patient subsequently alternated between moderately deep coma and moderate agitation, which appeared whenever he was stimulated by examination. On the following morning he appeared improved, drowsy but communicative, and made an uneventful recovery.

Comment.—This case illustrates one of the major uses of spectral differences to verify a tentative history. In this case, the only known medication to which the patient had access was a combination of methamphetamine and phenobarbital. His clinical picture at times resembled amphetamine poisoning, but at other times, when he was deeply comatose, the possibility of additional barbiturate ingestion was suggested. The blood level was in a range which could be extremely serious for a short-acting barbiturate but one from which recovery would be expected in the case of a long-acting barbiturate. By doing the spectral differences the clinician was able to obtain objective verification of the history and quantitative data which enabled him to select conservative therapy with confidence.

Acute Salicylate Intoxication

CASE 7.—A 45-year-old white woman with intermittent depressions for 10 years and a history of probable rheumatic fever was admitted to Georgetown Hospital after ingestion of seventy 300 mg. acetylsalicylic acid tablets between 3 p. m. and 4 p. m. At 4 p. m. the patient started vomiting and did so several times before gastric lavage was carried out at 6 p. m. The patient was drowsy and confused and had ringing in the ears, but respirations were normal. The urine ferric chloride test was markedly positive, but the serum acetone was negative, and the CO_2 was 37 vol. %. The blood salicylate level was found to be 45 mg. %. The patient was treated with intravenous lactate and fluids and oral sodium bicarbonate and made an uneventful recovery.

Comment.—This is an example of a moderately severe salicylate intoxication which responded well to conservative therapy.

CASE 8 (RD-105).—A 31-year-old white divorcee was transferred to Georgetown University Hospital in July 1955, with a history of having ingested 500 standard 5 grain (0.3 gm.) acetylsalicylic acid tablets while in an acute reactive depression. After first threatening to take the acetylsalicylic acid, the patient apparently went to her room, dissolved the acetylsalicylic acid tablets in water, and drank the water. She was taken to the District of Columbia General Hospital, where the blood salicylate level was found to be 95 mg. % and the prothrombin time, prolonged. No tablets were recovered by gastric lavage, and she was sent to a medical ward in an apparently good condition. Four hours after the approximate time of ingestion, the patient showed only apprehension, tachycardia of 104, moderately deep respirations of 26, temperature of 99 F, and a blood pressure of 150/90. Her face was slightly flushed and her reflexes hyperactive. All other laboratory tests were normal, and intravenous fluids were started consisting of dextrose and water, dextrose and saline, and M/6 lactate. Seven hours after ingestion, it was noted that her blood pressure had fallen to 94/70 and her pulse had increased to 124. Respirations were very much deeper, and the patient began developing hematomas at the site of needle injection and bled around the intravenous needle. Urinalysis revealed albumin of 1+, specific gravity of 1.028, and 15-20 red cells and 3-5 white cells per high-power field. She was transferred approximately 14 hours after ingestion. At this time she appeared wildly manic, was screaming, and had a blood pressure of 110/70. Respirations of 36 per minute were deep and Kussmaul in appearance, and her face and thorax were suffused and dusky. The prothrombin time was 46%, and the salicylate blood level at this time was 115 mg. %. A decision for dialysis was made, but the patient was screaming so wildly that cannulation was impossible. She was given 10 cc. of paraldehyde intramuscularly and immediately lapsed into deep coma without response to pain or light reflex. The blood pressure was maintained by levarterenol, and dialysis was begun at 16½ hours from the time of ingestion. Flow rates of 350 to 400 ml. per minute were obtained. Rectal temperature, which was rising, began to do so precipitously, and, while we began immediately to pack the patient in ice, the temperature continued to rise to 107.4 F. This was reduced to a

slightly hypothermic level by the ice-packing regimen. After 70 minutes of dialysis voluntary movement of the eyes were noted. At one and one-half hours she was groaning and retching. The patient gradually lost her tendency toward hyperthermia, gave calm responses, and began to talk. Throughout the dialysis, blood pressure was difficult to maintain and large amounts of levarterenol were required. Oozing was noted from all cut-down sites. There were tarry, diarrheal stools. The dialysis was stopped at a salicylate level of 29.5 mg. %. As the patient was disconnected from the machine, she vomited about 100 cc. of dark blood and was given 20 mg. of protamine and 100 mg. of vitamin K oxide. Postdialysis peripheral blood smear revealed adequate platelets, and the clotting time returned to six minutes. However, hematomas and oozing from the cut-down areas continued. Twenty-four hours later, with a normal clotting time, she continued to be a hypotensive problem and was oozing from all wound sites. On the following day, two convulsive seizures were noted, after which she had brief periods of apnea and cyanosis, constricted pupils, and stertorous breathing. The urine output remained low, and albuminuria continued. She was considered to have gastric and hepatic necrosis, nephrotoxicity, and cerebral damage, all due to salicylate. A hematoma developed at the cut-down site and had to be reexplored with careful hemostasis. During a period of apnea an endotrachial tube was inserted and artificial breathing was instituted, which resulted in considerable clinical improvement. Later the blood showed a coagulation defect and the following studies were done: Plasma recalcification time was 345, with a 130 control; plasma recalcification with three parts of the patient's serum and one part normal was 275; platelet count was 35,000; the prothrombin time was 21.2 seconds with a 14.5 control, and prothrombin comsumption was 15 seconds with a control of 115. Labile Factor SA was 35% to 40% of normal. The fibrinogen was normal. The impression of the hematologic consultant, Dr. Charles Rath, was that this represented multiple defects of the platelets, prothrombin complex, and other factors. She had by this time received a total of 21 units of blood in transfusion, including that used during dialysis. On the fourth hospital day the salicylate level was 6 mg. % and 2 units of platelet-rich blood were given. On the fifth hospital day the urine output reached 560 ml. and the platelet count was 10,000 after a platelet transfusion. The state of consciousness was remarkably improved; the patient had pain appreciation and normal pupillary reflex, and she began to speak a few words in response to questioning. Toward the latter part of this day it was noted that she was severely hyponatremic, with a serum sodium of 111 mEq., and an attempt was made to elevate this with hypertonic salt, but she became more comatose, and this was stopped. On the sixth hospital day she developed sudden apnea, did not respond to artificial respiration, and died.

Autopsy revealed acute red atrophy of the liver, multiple subendocardial ecchymoses in the left ventricle, multiple subepicardial ecchymoses in the left auricle, bilateral hydrothorax, subepithelial hemorrhage in the trachea and the right and left mainstem bronchus. One hundred cubic centimeters of hemorrhagic ascitic fluid was present in the peritoneal cavity. There was a massive intragastric hemorrhage with antemortem clot that weighed more than 60 gm. Mucosal hemorrhages were present throughout the entire intestinal tract. Hemorrhagic pelves in the left kidney, bulbous hemorrhagic cystitis, acute tubular necrosis, and inflammatory reaction suggesting pyelonephritis were noted. Subendometrial hemorrhages in the uterus, severe intrauterine hemorrhage, and hemorrhage into the broad ligament were seen. Multiple ecchymosis of the skin involved both arms from the hands to the shoulder girdle; massive ecchymosis involved the lower quadrant of the abdomen and groin, extending through subcutaneous fat and abdominal musculature to the peritoneum. Massive retroperitoneal hemorrhage extended from the diaphragm to the pelvis, confluent with the lower abdominal hemorrhage. The cause of death was acute salicylate intoxication with acute red atrophy of the liver, renal insufficiency, and massive multiple hemorrhages.

Comment.—Although this patient had a good initial clinical response to dialysis, it was felt that the period of exposure to a high salicylate level had been too long, and she died from a bleeding tendency which was, we believe, attributable to the acute red atrophy of the liver. Evidence of gastric, capillary, and renal pathology was also present. Severe hyperpyrexia from the salicylate may have played a role in the pathogenesis of these lesions, although salicylate, even in relatively low dosages, has been reported to produce a hemorrhagic diathesis.[39]

CASE 9 (RD-160).—A 21-month-old infant in good health procured methylsalicylate (wintergreen oil) liniment and ingested an estimated 30 ml. of this solution. He remained well for three hours, then complained of abdominal pain, vomited bloody material, and lapsed into hyperventilation. He was admitted to another hospital where gastric lavage was carried out, and he was given sodium bicarbonate. He was transferred to Georgetown as an emergency at 7 p. m. on Sept. 28, 1956, at

which time he appeared semicomatose, with a blood pressure of 70/35, respirations of 58 which were extremely deep, flushed hot skin, a body temperature of 104 F, pulse of 160, and markedly hyperactive reflexes with a positive Babinski on the right side. There was an odor of wintergreen on his breath. There were albuminuria, acetonuria, and a leukocytosis of 17,600. Prothrombin was 70% of normal. He deteriorated into flaccid coma, and a decision was made for dialysis. Arterial cannulation was performed by Dr. Charles Hufnagel, and dialysis was begun at 9:20 p. m., 80 minutes after admission to the hospital. The flow rate was surprisingly good from this small vessel and averaged about 50 ml. per minute. After 20 minutes of dialysis, the respiration slowed to 48, blood pressure was 60/30, pulse rate was 184, the temperature had dropped to 100, and the plantar reflexes became normal. The details of blood level changes and bath recovery are presented in Figure 5. Note the remarkable lowering of blood salicylate level from 110 to 29 mg/100 ml. This was accompanied by marked clinical response. The patient became alert and made an uneventful recovery, with clearing of an initial albuminuria. There were no apparent residual neurologic changes except weakness of one hand, and it was felt that dialysis substantially contributed to the survival of this case of severe methyl salicylate poisoning.

Case 10 (TC-52).—A 37-year-old housewife was admitted to Georgetown University Hospital in October 1957, with a history of having ingested 150 standard 5 grain acetylsalicylic acid tablets approximately six hours before admission. It was known that she vomited shortly thereafter. She was admitted to another hospital, where stomach lavage was carried out and fluid administered; then the patient was transferred. On arrival she was in a semicomatose condition and delirious. There was deep breathing, tinnitus, and deafness. She had a past history of family difficulty and depression and of poisoning due to acetylsalicylic acid, which had necessitated hospitalization.

On physical examination the temperature was 98.8 F; pulse, 100; blood pressure, 98/68, and respirations, 26 and deep. The patient was confused and very nervous and agitated, and she complained of the deafness and ringing in her ears. Initially she was handled conservatively with alkalinization and fluid. The ferric chloride test was markedly positive, and the urine volume was good. The initial blood salicylate level, however, was 101 mg. %, and because of this we felt that this patient was likely to develop further toxicity. Accordingly, a decision was made for dialysis, and the changes in blood salicylate during the dialysis are detailed in Figure 6. After dialysis, the patient became alert and stated that she was thinking much more clearly. Ten to fifteen red cells and one to two white cells appeared in the urine, but the temperature returned to normal, and the patient made an uneventful recovery.

Acute Bromide Intoxication

Case 11 (TC-4).—A 45-year-old white housewife was admitted in an agitated semicomatose state, with a history of having consumed tablets containing acetanilid and sodium bromide (Bromo-Seltzer) for epigastric distress. It was estimated that she had used two bottles (94 mEq. of bromide per bottle) in the seven-day period previous to admission. She had also chronically ingested one bottle of a drug containing potassium, sodium, and ammonium bromide (Nervine) per week (4 mEq. of bromide per teaspoon [4-5 ml.]). Sixteen days previous to admission, she consulted her physician for a "tired feeling," insomnia, and a suspected anemia. As is often the case, she was treated for the early symptoms of bromism by bromide itself and was given a prescription containing sodium bromide, 25 mEq. per bottle. She had used at least one and possibly two such bottles. Her past history was positive for recurring headaches, nervousness, periodic drinking, and a peptic ulcer syndrome. Her present illness began about two weeks previous to hospitalization, when she had dizziness, loss of depth perception, ataxia, and neglect of hygiene and housekeeping. When admitted to another hospital she was confused, irrational, and disoriented. She lapsed into a deep sleep interrupted by bursts of hallucinations and combativeness. Diagnoses considered were organic psychosis, schizophrenia, and brain tumor. A spinal fluid examination, however, revealed a NaBr level of 33 mEq. per liter, and serum bromide levels were reported at 43 and 36 mEq. per liter. She was transferred for possible dialysis because of the bromide level. (Goodman and Gilman state that bromide levels in the range of 19 to 25 mEq. per liter mean severe poisoning and those approaching 40 mEq. per liter are life-endangering.)

Physical examination revealed a well-developed gaunt woman with agitation, auditory and visual hallucinations, paranoid delusions, incoherent speech, pale dry skin, a beefy red smooth tongue, and a tachycardia of 100. Blood pressure was 120/78; respirations, 16, and temperature, 101 F. She had a palpable liver and markedly hyperactive deep-tendon reflexes. Her bromide level in our laboratory was 36 mEq. per liter. She was dialyzed on a twin-coil kidney for a period of six hours, and during the last hour, 3300 ml. of saline was infused at a rapid rate into a femoral catheter, and high-pressure filtration was employed. A total of 370 mEq. of sodium bromide was recovered in the dialysis bath and 1.5 mEq. in the urine. The patient remembered a few events in the fifth hour of

dialysis but remained psychotic for some 27 hours. The electroencephalogram prior to dialysis revealed bursts of Δ-activity generally, especially in the right parietal area. The dominant rhythm was about 9 per second. High-voltage slow activity was found throughout the tracing from time to time, especially in the parietal leads, with occasional 2-per-second slowing in the frontal region. The postdialysis EEG pattern showed a dominant rhythm of 11 per second and was considered normal. The α-rhythm was well organized, regular, and constant. Spiking was not found, and slow waves did not occur. Amplitude asymmetry was not evident in either hemisphere. Details of blood and spinal fluid bromide concentrations are presented in Figure 7. The patient made a rather abrupt recovery, remembering the specific moment of her return to rationality. However, she did show some minor periods of confusion in subsequent hours and was discharged in good condition from the hospital. She has been followed subsequently for over two years and has made an apparently complete recovery.

Acute Diphenylhydantoin (Dilantin) Poisoning

CASE 12 (TC 38).—A 2-year-old Negro boy was admitted to Georgetown in August 1957, in a stuporous state with a history of presumed ingestion of diphenylhydantoin sodium. The patient, together with three other children, was found staggering and drowsy after being awakened from a nap. A broken bottle of diphenylhydantoin sodium, which had contained more than 100 tablets, was found outside the house, with scattered tablets on the ground. Apparently the children had played hospital, and a total of 11 children ingested the drug. Six were treated at home and remained in good condition; three were treated at Children's Hospital in less serious condition; and two, including this patient, appeared most serious. On admission to Children's Hospital, the patient had deep stupor, poor response to painful stimuli, and hyperextension and stiffening episodes but no localizing signs. On arrival here, the patient was in deep stupor with episodes of hyperextension and short periods of apnea but no depressions of respiration in between. The liver was palpable. Blood pressure was 80/40; hematocrit, 36, and sickle-cell preparation, negative. The stupor deepened, and the blood pressure progressively decreased. The patient was connected to a single coil of the twin-coil kidney and dialyzed for three and one-half hours, with an average flow rate of 200 ml. per minute. The blood pressure was maintained at 110/50. The most significant changes during dialysis were decreasing, and finally absence of, opisthotonic attacks, some lightening of depression, with an increased irritability in the patient. There was some response to strong painful stimuli but no response to the spoken voice. The temperature decreased from 103 to 100 F. About four hours after dialysis, the blood pressure began to fall again; and the patient had to be maintained on levarterenol. Electroencephalogram on the following day showed slow activity with little cortical activity present. The patient had a seizure with spike-and-wave complexes throughout. The record was almost completely flat. A follow-up electroencephalogram taken two days later showed good organization and the basic frequency of 5 to 6 per second with no seizure discharges present. Clinically the patient was maintained on levarterenol and had a return of the opisthotonic episodes. These were controlled with trimethadione (Tridione). For almost a week the patient remained depressed but gradually became more responsive, with a type of fugue state where he sucked his thumb, lay quiet and relaxed, but did not speak or respond. He developed a hyponatremic syndrome with serum sodium falling to 115 mEq. per liter, but he responded to sodium repletion and made an uneventful recovery. He was discharged on the 26th hospital day.

We do not have too much confidence in the clinical measurement of diphenylhydantoin in the serum. However, the relative numbers may have some merit, and they were 11.6 before dialysis and 7.9 after dialysis. We have not yet been able to get measurements on the bath fluid.

Comment.—We conclude that definite clinical response was shown during the dialysis of this patient with severe diphenylhydantoin poisoning and marked cortical depression which was probably within the fatal range. The return of symptomatology after an interval of clearing suggests feedback from a tissue reservoir, which is in keeping with the known pharmacology and distribution of diphenylhydantoin. In such cases, it would probably be more advisable to dialyze for longer periods of time or at frequent intervals interrupted by equilibration periods.

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Georgetown University School of Medicine, Department of Medicine and Renal Laboratory.

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Peritoneal Dialysis and Newer Methods of Intestinal Perfusion in Renal Failure

PAUL R. SCHLOERB, M.D., Kansas City, Kan.

Because qualified personnel and necessary equipment are not universally available for the use of hemodialysis in the complications of acute renal failure, evaluation of other methods for the management of this problem is appropriate. The purpose of all methods of dialysis is the selective removal of retained metabolites, with correction and maintenance of water and electrolyte homeostasis. This is achieved in greater or less degree by gaining access to and modifying the composition of extracellular fluid. Cellular membrane transfers extend these beneficial effects to favorable changes in body composition.

During the oliguric phase of acute renal failure, potassium intoxication and pulmonary edema are the greatest potentially lethal factors.[1] Hyperpotassemia is accentuated by acidosis which is related to accumulation of anions, including phosphate, sulfate, and organic anions. Measures to correct this metabolic acidosis by withholding chloride ion, by allowing the extracellular chloride concentration to fall,[2] and by administering sodium with a disposable anion may prevent or reduce the hazard of toxic hyperpotassemia. Sodium must be given judiciously, of course, because of danger of precipitating pulmonary edema. It was shown long ago, however, that survival of bilaterally nephrectomized dogs could be prolonged by overhydration with production of edema.[3]

A progressive fall in plasma chloride concentration should not be cause for chloride replacement during the oliguric phase unless gastric chloride losses require correction of metabolic alkalosis.[2] Alleviation of hyperpotassemia by dialysis occurs not only by removal of potassium but by removal of excess anions, which tends to correct the acidosis and thereby reduces the predisposition to cellular egress of potassium.[4] Removal of potassium alone without removal of the anions represents less than the ideal; but potassium removal, together with development of hypochloremia, will help attain the over-all objective of correction of toxic hyperpotassemia and acidosis.

Urea is generally considered to be nontoxic, and its removal may even delay diuresis. The accumulation of relatively small amounts of other organic metabolites, such as phenols, guanidine, catecholamines, conjugated corticosteroids, creatinine, and uric acid, has not been proved to be a specific lethal factor in the uremic syndrome, although the contribution of phenols and guanidine to the symptomatology seems probable.[5]

The major chemical objective in acute renal failure, therefore, is removal of potassium in order to reduce extracellular concentrations and prevent death from this cause during oliguria. Secondarily, the removal of retained anions and organic metabolites by artificial means apparently will make the clinical course more benign, while water removal will alleviate pulmonary edema. These latter objectives, as well as potassium removal, can be accomplished most efficiently by hemodialysis but also by

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peritoneal dialysis over a longer period of time. Water and potassium removal and correction of acidosis by sodium absorption and chloride removal are achieved by intestinal perfusion; significant removal of phosphate, sulfate, and organic anions is not attained.

In advanced chronic uremia the chemical objective is prolonged maintenance of water, electrolyte, and nitrogen homeostasis, together with removal of sufficient retained anions and organic metabolites to simulate an acceptable degree of functional renal compensation. This implies the frequent repetitive use of a dialyzing procedure which can be done by the patient at home with minimum laboratory control. These latter conditions exclude the use of either hemodialysis or peritoneal dialysis from consideration and encourage the investigation of intestinal exchange for the attainment of these objectives in chronic uremia.

It is the purpose of this paper to present briefly a modified method of peritoneal dialysis and to summarize some newer approaches to the method of intestinal perfusion in acute renal failure as well as in chronic uremia.

Peritoneal Dialysis

Use of the 2 square meter surface area of peritoneum as a semipermeable membrane has been reviewed by Grollman [6] and by Merrill.[7] Although not as efficient as hemodialysis, the chemical end-result can be the same; but a longer time is required to effect comparable improvement.

Of all attempts to maintain animals after bilateral nephrectomy, the use of intermittent peritoneal dialysis by Houck [8] has resulted in the longest survival of one dog (for 111 days). For the first 70 days this animal was maintained adequately, requiring only occasional blood transfusions for anemia. This remarkable result, while representing a great expenditure of personnel, time, and effort, has not been equaled or even approached by any other form of treatment. Its use in a patient for 26 days has been reported.[9]

For the occasional application of peritoneal dialysis, practical considerations imply that this will be done without special training by a physician who must rely upon the materials commonly available in the average hospital central supply room. Usually this procedure will be done for acute reversible renal failure with hyperpotassemia and perhaps some overhydration.

The chemical problem is one of removal of potassium and organic anions with osmolal and electrolyte concentrations of the dialyzing fluid designed to prevent absorption of water and electrolytes. Table 1 lists the composition of a solution found suitable for this purpose and resembling that used by others, with the following exceptions: Potassium and magnesium are omitted in dialyses for acute renal failure, since adequate evidence exists that plasma concentrations of these ions are usually increased. The concentration of chloride is lower than the normal plasma value but probably rep-

TABLE 1.—*Fluid Composition for Peritoneal Dialysis* *

A. Ionic and crystalloid composition	mEq/L.
Na	135
K	0
Ca	5
Mg	0
Cl	80
HCO_3	27
Lactate	33
Glucose	27.6 gr.
Tetracycline	100 mg.

B. Preparation of each liter from sterile stock solutions	Ml.
1. 5% glucose in 0.85% saline	516
2. M/6 sodium lactate	198
3. 10% calcium gluconate	10
4. 50% glucose	3.6
5. 500 mg. tetracycline in 20 ml.	4
6. Sterile water (q. s. ad. 970 ml.)	238
7. 7.5% sodium bicarbonate	30

* Sodium bicarbonate is added prior to use. Osmolality is 450 per liter. Graduations on the 1 liter infusion flasks may be used to approximate the above amounts of glucose in saline, sodium lactate, and water with sufficient accuracy. Sterile syringes are used to measure the other components. Additional glucose will increase the rate of water removal. Each 16 gm. of glucose equivalent to 100 mOsm/kg. of water in the above solution.

resents a more desirable concentration for the uremic patient with acute renal failure because of retention of fixed anions. The lowered chloride concentration helps prevent the development of "chloruremia"[10] and acidosis which have been observed[9] with higher chloride concentrations. Removal of excessive amounts of potassium or magnesium will not occur in the usual peritoneal dialysis procedure for acute renal failure by omission of these electrolytes. Assuming equilibrium of the peritoneal dialysate with plasma, total body potassium would be decreased only about 0.2% by each liter of dialyzing fluid. Prolonged dialysis over a period of days would, of course, require the addition of potassium, magnesium, and additional chloride to prevent depletions of these substances. Only rarely is this a practical consideration, however. Phosphate and sulfate are not used because of retention of these anions.

The intermittent technique employed is similar to that proposed by Grollman,[6] who reports that continuous perfusion has no advantage over intermittent infusion-aspiration and may result in undesirable peritoneal fluid accumulation as well as extravasation into the abdominal wall with absorption if the outflow tract becomes obstructed by omentum or bowel. The dialyzing fluid, prepared in 1 liter intravenous infusion flasks, with use of sterile technique, is connected through disposable intravenous infusion tubing to a 14-gauge needle. After local infiltration with 1% procaine, the abdominal skin is entered through the left flank, and the tubing clamp is removed, resulting in a slow drip of fluid. The needle is advanced slowly, and entry through the peritoneum is signaled by a marked increase in rate of flow, when the fluid is allowed to run in as rapidly as possible (about 100 ml. per minute). I have not observed bowel perforation or bleeding in patients or in the laboratory with use of this method of paracentesis. One hour after the infusion of as much solution as is tolerated symptomatically (2 to 4 liters in the adult), a trocar is inserted in the midline and a sterile polyvinyl tube of the type employed for feeding tubes is inserted about one foot and, after removal of the trocar, it is connected through another plastic tube to a flask on the floor in the manner described by Grollman.[6] Drainage is allowed to occur and may be increased by change of position of the patient, abdominal massage, and momentary elevation of the outflow tube. Recovery of the infused fluid is a time-consuming procedure, and leakage of some fluid around the catheter makes precise volume measurements difficult. Use of a "scissors" technique for paracentesis does not preclude fascial and subcutaneous extravasations of peritoneal fluid with absorption. It is considered preferable, therefore, to accept the nuisance of external leakage. This fault does not necessarily outweigh the advantages to be gained, however, and body weights before and after dialysis afford an index of water transfer. After drainage of the approximate amount instilled, another 2 to 4 liters is infused, and this cycle is repeated for about 12 hours. At the end of this time, 100 mg. of tetracycline are instilled, and the catheter is removed. This may be repeated daily as circumstances require such adjunctive management. Sufficient potassium may be removed with partial correction of acidosis in one day to permit continuation of other therapy until diuresis ensues. Because of the hazard of infection the catheter should not be left in place for longer than one day. The source of infection has been shown to be due to migration of bacteria through the bowel wall,[11] and the foreign-body reaction to even a relatively inert plastic catheter would be expected to aggravate this process.

Peritoneal dialysis may have occasional application in the adjunctive management of acute renal failure, chiefly for the correction of hyperpotassemia, with some correction of acidosis, water removal, and reduction in azotemia as well. Simplicity and availability of materials make it suitable for use by physicians qualified to manage adequately the other phases of acute renal failure. Except for the concurrence of bleeding, which

would contraindicate necessary heparinization for hemodialysis, its use in perference to extracorporeal hemodialysis can hardly be justified when a dialyzing apparatus and team are available, since the possible complications of peritoneal dialysis are greater and the efficiency is less.

The time required, need for professional personnel, expense of sterile solutions, patient discomfort, possible complications (including peritonitis), and the necessity for hospitalization preclude its frequent, repetitive, and indefinite use in advanced chronic uremia.

Intestinal Perfusion Methods

Intestinal perfusion has been employed to remove uremic metabolites and to maintain water and electrolyte homeostasis, as reviewed by Twiss [12] and more recently by Merrill.[7] Behavior of the intestinal mucosa as an active rather than a passive semipermeable membrane with regard to electrolytes has engendered some difficulty in the composition of perfusate solutions, but it is generally agreed that physiologic conditions for desired water and electrolyte transfers exist, while sufficient nitrogen, chiefly as urea, may be removed in uremia to maintain over-all nitrogen balance with moderate azotemia. It is also well established that phosphate, uric acid, creatinine, and probably other larger-molecule uremic metabolites are not removed in sufficient quantities to lower plasma concentrations significantly.

The management of potassium intoxication by intestinal perfusion has not only been effective, but, according to one report, potassium depletion resulted from intestinal perfusion in which potassium was omitted from the perfusate.[13] I have removed 7 mEq. per hour by perfusion of the entire bowel. It therefore seems probable that hyperpotassemia accompanying acute renal failure may be corrected by intestinal perfusion. While adequate amounts of urea can be removed, this is not necessarily desirable in acute renal failure, since urea is probably nontoxic, and the increased plasma osmolality resulting from urea retention may actually promote earlier diuresis.[7] No evidence that creatinine is toxic exists, and plasma uric acid concentrations would be expected to increase at a rate of only 1 mg. % per day with anuria. Possible toxic effects of other uremic metabolites such as phenols, guanidine, and others have not been defined clearly, but bacterial action in the intestinal tract has been established as the source of some of these.[5]

In acute renal failure, intestinal perfusion may be used to combat hyperpotassemia by removal of potassium and chloride and by producing some sodium absorption, together with removal of urea but not significant amounts of other uremic metabolites. Practical considerations such as nausea and vomiting limit its application, and gastrointestinal surgery, ileus, or any condition predisposing to gastrointestinal hemorrhage contraindicate its use.

Reported methods, reviewed by Twiss [12] and by Merrill [7] together with more recent additions, are listed in Table 2. Removal of uremic metabolites by gastric or duodenal aspiration is limited by the relatively small volumes available. Perfusion of the large bowel through an appendicostomy or the use of enemas may be helpful in removing potassium, but nitrogen removal is negligible. Gastric lavage may be complicated by vomiting and unpredictable diarrheal losses.

TABLE 2.—*Methods for Gastrointestinal Removal of Uremic Metabolites*

1. Gastric or duodenal aspiration
2. Gastric lavage and enemas
3. Ion-exchange resins, orally and as enemas
4. Intubation with a multiple-lumen tube with jejunal perfusion and ileal aspiration
5. Duodenal or jejunal perfusion with appendicostomy aspiration or rectal collection
6. Appendicostomy with large bowel perfusion
7. Isolated ileal or midintestine segment perfusion
8. Gastrostomy with pyloric intubation and perfusion of the entire bowel with rectal collection
9. Perfusion of a cellophane tube placed within the small intestine by jejunostomy (enterodialysis)
10. Perfusion of a semipermeable-membrane balloon in the stomach (gastrodialysis)
11. Perfusion of isolated proximal half of the small intestine (jejunal segment)

Oral use of ion-exchange resins is difficult in the presence of nausea, and constipation has been an undesirable sequel. Resin enemas have been reported to remove 21 to 73 mEq. of potassium per day [14] but are also said to produce impaction.[7]

Intubation of the small intestine beyond the ligament of Treitz by any type of tube will result in the bowel being milked up on the tube by peristalsis, with decrease in available mucosal surface area. This is a common operative finding in patients having laparotomy with prior intubation of the intestine with a long tube. As a temporary expedient, however, intubation and perfusion of the bowel with a multiple-lumen tube may be quite effective. Removal of potassium at a rate of 62 mEq. in 10.5 hours was accomplished in one such study.[15] Peroral intubation and perfusion of the duodenum and distal collection of the perfusate by either appendicostomy aspiration or a rectal tube obviates the objection of using a long tube within the small bowel. It has been found that appendicostomy aspiration does not prevent rectal drainage, however.

I have found gastrostomy to be an effective way to permit frequent intubations of the duodenum for intestinal perfusion in chronic uremia, and this has been used for administration of nutrients and medications into the stomach as well. A relatively minor surgical procedure, it has been done under local anesthesia in critically ill patients. The discomfort of a tube in the nose and fluoroscopic manipulations to intubate the pylorus are thereby obviated.

Perfusion of a semipermeable membrane bag in the stomach (gastrodialysis)[16] and a closed cellophane tube in the intestine (enterodialysis)[17] have been evaluated by me during the past three years. Study of gastrodialysis in a normal subject, nephrectomized dogs, and three uremic patients showed that 72 mEq. of potassium but only 3 gm. of nitrogen could be removed each day. Transfer of potassium as well as water, sodium, chloride, and hydrogen suggests its application to the management of hyperpotassemia, acid-base derangements, and hyperhydration disorders. These transfers occur relatively slowly, however, so that I have not yet felt justified in attempting to correct severe hyperpotassemia by gastrodialysis when a hemodialyzer is easily available. While the transfers of potassium suggest application of gastrodialysis to the prevention of hyperpotassemia associated with acute renal failure, this has not as yet been a practical consideration in my experience with the management of acute renal failure by the dietary and fluid-electrolyte measures employed.

Laboratory investigation of exchanges and transfers between the blood and the lumen of a cellophane tube within the intestine has resulted in the application of this method to one patient with terminal uremia.[18] Seven feet of $^{27}/_{32}$ in. diameter cellophane were inserted by jejunostomy, and perfusion of the cellophane tube was done. Potassium was removed at a rate of 36 mEq. per day, and nitrogen was extracted at a rate of 12 gm. per day, with temporary improvement. Except for its use in correction of water and electrolyte derangements and administration of nutrients, cellophane-tube perfusion at present has no apparent advantage over direct perfusion, although evaluation is continuing.

Perfusion of an operatively isolated ileal segment was first done by Kolff,[19] and subsequent patients have been reported.[20-23] For the past 18 months I have studied the clinical application of perfusion of an operatively isolated jejunal segment comprising the proximal half of the small intestine.[24] This experience now consists of four patients, two of whom died in uremia without more than slight and temporary benefit from perfusion of the isolated segment. Of these two patients, one was complicated by the combination of overwhelming sepsis and uremia, while the second patient, following an uncomplicated operative procedure, was observed to have only minimal exchange of water, electrolytes, and crystalloids across the intestinal mucosa during the isolated in-

testinal segment perfusions. This decreased exchange may have been related to marked arteriolosclerosis in the submucosal vessels, as demonstrated at autopsy.

One 18-year-old patient * with chronic glomerulonephritis and advanced uremia was maintained in the hospital for 10 weeks by 50 perfusions of an isolated jejunal segment. With use of 32 different perfusate compositions with wide ranges of electrolyte concentrations and osmolality, the transfer rates of sodium, potassium, calcium, magnesium, chloride, urea, water, and other substances were determined and were related to the perfusate concentrations. Water exchange was investigated with deuterium oxide.

At a flow rate of 2 liters per hour, the perfusate concentrations at which no transfers of electrolytes occurred were also related to the serum concentrations. This perfusate contained about one-third of the normal plasma sodium and chloride and double the normal plasma potassium concentration, with additional calcium and magnesium. Urea nitrogen was removed at a rate of 0.8 $\pm$0.3 gm. per hour, and total body urea was reduced by 12.8% $\pm$6.5% of its initial value by each perfusion.

In this patient with progressive oliguria, maintenance of water and electrolyte homeostasis was feasible by appropriate adjustments of the perfusate composition. Application of this information permitted subsequent management for one month at home where 24 additional perfusions were done until anuria and fatal uric acid intoxication occurred. These data are being reported in detail elsewhere.

Another patient † is a 26-year-old woman with polycystic kidney disease. She had progressive azotemia, weight loss, hypertension, hypertensive retinopathy, and weakness which prevented full-time employment. Over one year ago an isolated jejunal segment procedure was done and was well tolerated. The blood urea nitrogen on admission was 88 mg. % and was 61 mg. % on discharge. Since that time, with brief weekly perfusions at home to wash out the segment, she has experienced clinical improvement and is able to work full time. Reevaluation recently (one year after operation) indicated moderate progression of the azotemia, but she had gained tissue weight and felt well. Reevaluation of the electrolyte, water, and nitrogen transfer rates by the isolated jejunal segment revealed no deterioration of function during the one-year interval. Although small amounts of discharge occur from the abdominal stomata and small amounts of uremic metabolites are removed in this way and by the brief weekly perfusions, it is difficult to quantify the tissue-weight gain, increased well-being, and regression of hypertension and hypertensive retinopathy on this basis. Electrolyte, water, and nitrogen transfers permit an approach to these phases of the uremic syndrome as clinical symptoms warrant.

In contrast to other methods used for dialyses in acute renal failure, perfusion of an isolated intestinal segment appears to be the only method presently available for the adjunctive management of progressive chronic uremia over a long period of time by the patient. Total renal function is not attained because of failure to remove adequate amounts of phosphate, creatinine, uric acid, and probably other larger uremic metabolites. It will otherwise defend the composition of the extracellular fluid and, indirectly intracellular constituents as well as body water, and will remove sufficient urea to maintain an acceptable nitrogen economy. The use of commonly available salts, sugar, and tap water, together with nonsterile perfusion carboys and tubing, make it an inexpensive procedure. Discomfort related either to the presence of the isolated segment or to the perfusions has not been observed.

The indications for isolated jejunal segment perfusion remain to be defined. It is

* Referred by Dr. John MacMillan, Idaho Falls, Idaho.

† Referred by Dr. Elmer Belt, Los Angeles.

believed, however, from my experiences thus far that this may be of benefit to young patients with progressive renal disease. Kidney disease, associated with widespread arteriolar changes which include the vessels in the intestinal segment, may limit mucosal transfer and exchange. Polycystic kidney disease would appear to be an ideal condition to which isolated jejunal segment perfusion might be applied when renal decompensation and hypertension become evident on good management and before severe uremia has developed.

Summary and Conclusions

Associated infection or other complications of acute renal failure may require the use of some form of dialysis. Peritoneal dialysis may be done if hemodialysis facilities are not available or if transportation of the patient is not feasible. The desirability of its elective use to moderate the clinical course of the disease must be weighed against its possible complications and the 85% survival obtainable by dietary and fluid-electrolyte measures alone.[25]

Duodenal perfusion with the proper perfusate is an effective way to remove potassium and water in acute renal failure, but intubation of the pylorus, especially in the presence of vomiting, limits its use, and it is not applicable to conditions associated with ileus, gastrointestinal surgery, or incipient bleeding. Sodium lactate-glucose enemas, resin enemas, oral resins, and perfusion of a semipermeable-membrane balloon within the stomach (gastrodialysis) may also be useful for removal of potassium.

Neither extracorporeal hemodialysis nor peritoneal dialysis is suitable for frequent repeated use in patients with advanced chronic uremia. Clinical experience with perfusion of the operatively isolated jejunal segment indicates that, while all uremic metabolites are not removable, body water, electrolyte, and nitrogen homeostasis can be achieved and that this can be done by patients at home with minimum laboratory control. Results thus far in this continuing study suggest that this procedure should be evaluated further, especially in young adults with intractable progressive renal disease.

University of Kansas Medical Center, Rainbow Boulevard at 39th St. (12).

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The Education of an Internist

A. M. SNELL, M.D., Palo Alto, Calif.

The launching of space satellites by the Russians in the autumn months of 1957 has instigated one of the most widespread and most severely critical examinations of the American educational system in its history. Our own successes in the satellite field at a somewhat later date have done little to alter the activity of the critics who have aimed their darts not only at the elementary schools but even at the citadels of higher learning. No one has, to my knowledge, suggested that the Russians have topped us in the field of medical science, but a recent exchange of visitors between the two countries leads one to believe that they have elevated their previous level of medical activity very considerably. With the abovementioned activities fresh in mind, it seems appropriate for the Chairman of the Section on Medicine to review the educational process by which our internists are trained. One may say at the outset that there is little fault to find with it and a great deal that may be rightly praised.

The internist of 40 years ago (which happens to be the date of my graduation from medical school) was a member of a relatively scarce specialty. Only about 1500 such specialists were listed in the directories of the period. Their medical background was frequently of European, and more particularly of German, origin, and Osler and and Virchow were their guiding luminaries. The internist of 1918 was, as a rule, well grounded in pathology, but the physiology of the era was somewhat outside of his domain. His diagnostic facilities were scanty and more often than not carried in his head and coat pocket. Most of his decisions were made on what he saw and heard at the bedside. He recognized the precomatose state in diabetes by the odor of the breath and the feel of the eyeball, not by blood chemical studies; heart disease was diagnosed by the stethoscope alone, since virtually the only use of the electrocardiogram at the time was in the study of arrhythmias. On most gastrointestinal complaints, he was able to make an educated guess on the basis of the history, with limited help from the radiologist. His therapeutic resources were equally slim. If one took away from him digitalis, morphine, quinine, mercury, iodides, and arsenicals, he was virtually destitute. He was, however, part of and related to the great past of medicine, and he diagnosed and treated almost all of the disease syndromes with which we now deal with a very considerable degree of skill. With his meager diagnostic and therapeutic equipment he made an exceedingly good showing and managed to hold his own very well at a time when surgery represented the more glamorous section of the medical profession.

In the years immediately preceding World War I, a new breed of internist began to appear. His principal interests were in clinical physiology, and his studies were often directed at measuring various bodily functions in health and disease. These men began a renaissance of learning in the field of medicine by substituting measuring sticks for impressions and exact information for the shrewd guesses of their predecessors. What has happened since need not be reviewed in detail. In the past 40 years there has been a tremendous extension of

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the body of medical knowledge along with a broadening and deepening of its scope. There has been concurrently a geometrical progression in the development of investigative and diagnostic methods. At the present time our medical curricula and our library shelves are replete with more and more detailed biochemical and physiochemical data pertaining to the pathologic physiology of disease. Therapeutic advances have almost kept pace; new drugs appear faster than they can be safely utilized to the point where every journal one reads calls attention to the harmful possibilities of a drug advocated two or three issues back. The gains which have accrued to the general health of the country and to the care of the individual patient because of the developments mentioned above can hardly be overestimated. Many diseases in the knowledge of which the internist of 1918 excelled have been virtually liquidated. In fact, if one excludes the degenerative diseases of age, cardiovascular-renal disease, and malignancy, there are not too many worlds left to conquer.

Whether the present-day internist has not lost something to counterbalance these impressive gains remains to be considered. His training is long and arduous; it is almost the rule that he has had more than one year's intership, three years of residency training, and a variable period of time devoted to an investigative problem, often one in a basic science. Much has been given to him, and correspondingly much is to be expected as he enters practice. He is the generalist of present-day medicine, and, in addition, his advice is sought in many specialized fields. It is the current fashion to refer to an internist almost any ailment to which flesh is heir for examination to see if there is an "underlying medical cause." He is a family medical advisor; he is consulted in public health matters; he is expected to provide advice regarding executive and other health programs; he is often a strong supporting arm to his surgical colleagues, and he is a sort of shock-trooper in group practice. It does not take our young internist long to recognize that his education is to be a continuing process and that he must grow as the field of medicine grows. As Liebow of Yale recently said, "Education implies growth, growth unlimited, autonomous and in perpetuity."

Is our present educational program adequate for the needs of this rapidly expanding field? There are those who feel that with all our newly acquired knowledge we have not yet achieved a wholly satisfactory goal and that there are still weaknesses in our attempts to produce physicians with a sound knowledge of the scientific method along with wisdom, critical sense, humility, and compassion, qualities which were no more highly valued 40 years ago than they are now.

How may one measure the quality of the product which our current methods of training internists produces? A final decision must rest upon the man's ability in caring for the patient and his usefulness to his professional colleagues as a consultant in his special field. These are areas not easily measured, but one's impression of our younger internists must be largely of a favorable sort. There is one hurdle which many of our young men wish to clear, and that is examination by the American Board of Internal Medicine. This much discussed and frequently criticized body has for the past 10 years examined about 1000 or more candidates annually by both oral and written techniques. The Board has labored mightily over the subject matter and methodology of these examinations, has endeavored to learn by both its failures and successes, and has done its conscientious best to make a fair, although searching, appraisal of a man's qualities to act as a consultant in the field of internal medicine. How well the Board has succeeded it is difficult to say; that these examinations have merit in the eyes of the profession is demonstrated by the importance attached to Board certification in this and, in fact, all medical and surgical specialties. One man's impressions after long service on the Board does not represent a

final judgement on the training of candidates, but it may be offered here as a tentative answer to the question previously proposed. Our good medical resident comes to Board examinations literally crammed with factual knowledge. Some of it he may not have fully mastered; some is simply undigested, and, finally, many of the clinical applications of this knowledge are still rather obscure in his mind. He has the equipment; he has had the lessons, and he has had a fair amount of practical experience, but, like many a Sunday golfer, he still has a relatively high handicap. The oral examination is the place where his difficulties most frequently come to light. Here the failure rate is higher than it should be; this appears to stem in the main from three things: (*a*) too early a concentration on special fields, with the result that many of the common syndromes encountered in the course of examination in a general hospital are seen through a glass darkly; (*b*) too firm a belief that the clinical, pathological, or x-ray laboratory will provide a diagnostic answer if only the right test or study is at hand, and (*c*) inability to make the most of the five senses in the study of the patient. The look, the odor, the sound, the "feel" of disease are somehow missed; physical findings, especially the significant little ones, are ignored or misinterpreted; a laboratory report is given precedence over some clear-cut clinical feature. Our candidate, in brief, has failed to develop the detective instinct which guided our medical forebears to so many correct diagnoses. He may have the general problem well in mind and could probably write a good discussion of it, but his clinical knowledge is not often arranged in neat workman-like packages ready for use, at least in solving riddles at the bedside.

Some of the difficulty goes back to weakness in the teaching of physical diagnosis. The late George Barnett, long-time clinical professor of medicine at Stanford University, was in the habit of reading to his classes portions of Voltaire's "Zadig." Those of you familiar with the story will remember that Zadig "studied above all the characteristics of animals and plants and soon acquired a perspicacity which showed him a thousand differences where other men see only uniformity." The narrative which follows concerning the story of Zadig's observations on the progress of the queen's bitch and of the king's horse could, I think, be profitably incorporated into any text bearing on the examination of the patient. Without the initially observing eye and the cultivated imagination of the mythical Zadig, medical knowledge cannot be properly brought to bear on the problem before us. What does it avail a man to know the metabolic activities of uric acid labeled with C^{14} if he does not recognize the clinical story and the physical aspects of gout? Of what use is knowledge of irradiated iodine uptakes if the skin and reflexes of the myxedematous or the thyrotoxic patient do not catch the eye?

It should not be inferred that all candidates are weak in respect to the clinical or bedside study of the patient; the pity of it is that so many of them are. They are, as a group, extremely well-grounded personable hard-working young men who have every right to expect success. Is the weakness one finds in bedside techniques their own fault? I prefer to think that it is not. The difficulty more probably lies in the system that makes our young internists come so far over so much newly discovered territory in so short a time—and frequently with too little guidance.

At this point we may inquire as to how the situation may be altered. Three phases of the program are to be considered: the medical school curriculum, the intern and residency program, and the entrance of our young internist into practice.

Above the gate of the University of Aberdeen there is an ancient motto, "They have said—what say they?—let them say," which is, of course, an expression of interest in the knowledge of the past, that of the present day, and that of the future. Others have

stated that the functions of an institution of higher learning were three—the preservation of knowledge, its dissemination, and the advancement of learning. Does the modern medical school fulfill these functions, which seem to many to be admirable? The emphasis has shifted heavily toward the latter function, as it has been bound to do during a time when the fields of human biology and medicine have expanded at such a phenomenal rate. Chairmen of the departments of medicine in this country are almost without exception men who have made solid contributions to medical and scientific knowledge and who are continuing their basic investigations into disease processes. Furthermore, the department of medicine now has well-established contacts with the more fundamental departments of universities and we have what has been called a hybridization of medicine with the whole field of biologic science. The end-result has been an educational process which appears to many to be excellent but somewhat lopsided. It is easier to get financial support for an investigative project than an endowment for a single clinical teacher. There is in many schools a definite shortage of such teachers and a neglect of methodology. The result has been that the student is called upon to accept more and more personal responsibility for the development of that side of his training which deals directly with the care of the patient.

The medical curriculum is currently the target of much criticism and the object of intensive study. To quote Liebow again, it is still "a bewildering jungle" in which "all originality is stifled under the falling closely printed leaves, and the student is deprived of the light of the outside world." Much that is taught is overly detailed, and time is lost on nonessentials. Furthermore, some of the detail may be purely ephemeral. The advancement of knowledge has been so great in the last four decades that there has been little time for sorting and evaluation of the medical harvest. If one reads any journal five or more years old, it is plain that a good deal of what was once believed to be legitimate currency has now been declared counterfeit. This is no new experience in medicine, a fact which Sir Thomas Browne recognized almost three centuries ago when he wrote, "We do but learn today what our better advanced judgments will unteach us tomorrow."

Then, too, the program of intern training has not escaped criticism. The more highly regarded the teaching hospital, the larger the number of the men who in a sense separate the intern from the final responsibility of patient care. He has as his superiors a junior, assistant, and chief resident; one or more attending staff men; a varying number of clinical investigators, and, finally, a professor or two. The system, while it has many things to recommend it, is likely to lead to a stifling of initiative and a dilution of the junior's sense of responsibility for patient care. He soon finds stout shoulders upon which he can lean and easy sources of practical information. These will be most sadly missed in his early years of practice when he is forced to become a "do-it-yourself" practitioner. Somewhat the same criticism has been offered in regard to residency programs; there is again a dilution of responsibility, often more or less proportional to the number of men concerned with the patient's care. Finally, it has been frequently noted that specialization in the residency program may come too soon. The young men with an investigative bent are often attracted or directed to special fields, and it is not uncommon for them to end their period of training having spent a great deal of time in what might be called the stratosphere of medical knowledge and very little at the grass-roots level.

The medical curriculum should be judiciously pruned and made more flexible with greater opportunity for the student to develop some of his own interests and capabilities. The great basic ideas in medicine and the fundamentals of anatomy, physiology, and pathology must be soundly taught and correlated with clinical medicine. It has

been said that "we may have to settle for a modicum of ignorance" in our graduates and allow the later training processes of the resident years to fill in some of the detail not previously mastered. There should be more clinical teaching by full-time men whose primary functions should be that of instructing at the bedside and in the clinic. These men should have a familiarity with the basic sciences, with medical history, and with current medical literature. There should be endowments for such teachers just as there are for the maintenance of clinical investigation. Such men may and frequently do furnish a connecting link between the ivory tower of the medical school and the practicing physician.

There is one other field in which it is believed that our medical educational system falls short. In our efforts to master the intricacies of our new knowledge we have not infrequently ended by taking much of the flavor out of medicine. Patients are not, as we have been reminded many times, elaborate experiments in pathological physiology set up for our edification. How can we know them better for what they are, human beings in real or fancied distress? Here a return to the study of literature, history, and the humanities may be recommended. The fictional characters who figure in many classical tales have largely been drawn from life; they are, in fact, all around us. Who has not seen Falstaff in the flesh, or Madame Bovary, Micawber, the wife of Bath, or the Pharisee in St. Luke's Gospel? To recognize these worthies you must occasionally renew your acquaintance with them. It is sacrilege to suggest it, but would not an occasional excursion into the classics, read once and forgotten, be as useful to our residents as an equal period of time devoted to the latest issue of the most highly regarded medical journal? The imagination needs stimulation as much as does the accumulative process of memorizing scientific data.

Finally, let us consider the progress of the recently graduated resident as he enters practice. Here for the first time he is made aware of the great gap which separates the teaching hospital and the workaday world of practice. The marvelously interesting and unusual cases in the wards are gone; in their place he finds patients with the most prosaic complaints. When the patient with something out of the ordinary does come along, as he does inevitably, where are the laboratory facilities of his training years? He learns to his sorrow that urinary gonadotropins and catechols, irradiated triiolein uptakes, and blood-ammonia determinations are not easy to come by. Then, too, he often finds that some of the routine laboratory work available to him is not of the quality provided by the more skilled technicians of his medical school. I am certain that many a budding young internist feels as the rich man Dives did in the parable when he called from his place of torment upon the beggar Lazarus in Abraham's bosom and heard from the patriarch's lips the answer, "Between us and you there is a great gulf fixed; so that they which would pass from hence to you cannot!"

Here is the test of the internist's mettle. He can do one of many things, the wisest of which is to learn to use his own five senses and to reacquire some of the arts of his medical forefathers. Furthermore, he may now begin to learn at first hand the natural history of disease and of its vagaries in the human species. His first great test is passed when he recognizes an organic disease concealed in a tangle of neurotic complaints; his second, when he has the courage to stick to a diagnosis made solely by his own resources and without the backing of the laboratory. Then it may be said that his education as an internist is fairly begun.

Is it ever completed? Not so long as he can observe, read, and speculate, not so long as he retains his interest in the out-of-the-ordinary case and in the necropsy findings that have proved him wrong. From this point on he should begin to store his mental images of disease as it is encountered in all manners and conditions of people, exactly

as one collects curios or incunabula; not as one banks money to be accumulated and later spent but as a permanent collection particularly his own. He is fortunate if he is able to transmit some of this personally acquired knowledge to others; of what use is a collection of anything if it cannot be exhibited occasionally?

The criticisms offered above and in these concluding paragraphs are not entirely my own. Many have appeared recently in *The Journal of the American Medical Association* in the form of reports from the Committees on Medical Education and Licensure. These comments, of course, do not apply to the training of internists only but to the general process of medical education. It now appears to many that we need a broader premedical education with emphasis on the humanities, even if this means a reduction in science courses. There should probably be less attention to grades, now almost the sole measuring stick, and more to attitudes of mind, natural aptitudes, and motivation. There is little danger that the progress of the scientific method will be retarded by such changes, nor is it likely that attempts to teach more of the older arts and skills of the profession will undermine the current urge for clinical investigation. In fact, the art of medicine and the spirit of research may be mutually stimulated by a closer rapport between their respective disciplines.

A final note concerns itself with the purely quantitative side of the problem. Are we training too many internists? So far as one can see at the moment the saturation point is not in sight. There are approximately 11,000 Board-certified internists in this country today and at least an equal number, possibly fully as competent, who have not sought Board certification. A great many have been absorbed by teaching institutions and perhaps an even greater number by the Federal medical services which probably have not as yet reached their peak growth. The rest seem to be extremely well distributed throughout the country. There is scarcely a town of any size which does not have a well-trained internist available, with sufficient laboratory and radiologic equipment to give him an opportunity to exhibit his special skills. The presence of these men in so many communities has, I am sure, furnished a great stimulus to the standards of medical practice. I do not wish to imply that they are necessarily "the little leaven that leavens the whole lump," but that they serve as effective catalysts can hardly be denied. The majority of them will remain in the combined status of family medical advisor and consultant to their professional colleagues in some special field. One suspects that the medicine of the future will demand more and better internists; let us look to our educational methods so that these needs will be well met.

Palo Alto Medical Clinic, 300 Homer Ave.

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Results of Mitral Commissurotomy

Follow-Up of Three and One-Half to Seven Years

F. HENRY ELLIS Jr., M.D.; DANIEL C. CONNOLLY, M.D.; JOHN W. KIRKLIN, M.D., and ROBERT L. PARKER, M.D., Rochester, Minn.

Ten years have passed since the first successful mitral commissurotomy was performed.[1] During these years countless such operations have been done by surgeons all over the world, and there have been many reports of the early results of this procedure. Long-term follow-up studies are essential in the evaluation of any operative procedure. Studies of this type that have been reported [2-8] indicate that the condition of between two-thirds and three-fourths of the patients operated on is improved. Now that it is possible to operate successfully on the open heart, it is more important than ever to evaluate the long-term results of a closed technique. The question will inevitably arise as to whether open-heart techniques should be used in the treatment of some or even all patients with mitral stenosis. With this in mind the present study was undertaken. The first 131 patients operated on at the Mayo Clinic, of whom there were 120 survivors of the postoperative period in the hospital, form the basis of this report.

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Section of Surgery (Dr. Ellis and Dr. Kirklin) and Section of Medicine (Dr. Connolly and Dr. Parker), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Short-Term Results

The early results of these 131 operations were reported previously [9] (Table 1). There were 11 operative deaths. Of the 94 surviving patients followed in the original study, 87.2% had an excellent result or achieved significant improvement. When the 11 operative deaths are included, operation was of benefit to 78.1% of the patients so treated. The follow-up period in this study varied from 3 months to 3 years, averaging 13.1 months.

Nature of Present Study

All 120 survivors of the postoperative period in the hospital, among the first 131 who under-

TABLE 1.—*Mitral Stenosis—Early Clinical Results in Patients Surviving Mitral Commissurotomy* *

Preoperative New York Heart Association Classification	Patients	Result, Number of Patients				
				Failure		
		Excellent	Significant Improvement	Late Death	Unimproved	Cerebral Residual
I	2	2	—	—	—	—
II	16	13	1	1	1	—
III	49	29	15	2	1	2
IV	27	15	7	4	1	—
Total	94	59 (62.8%)	23 (24.4%)	7	3	2

* Follow-up period ranges from 3 mo. to 3 yr.

went mitral commissurotomy at the Mayo Clinic, are included in the present study. Up-to-date follow-up information was available on all of these patients at the time of preparation of this report. Two thirds of them underwent reexamination at the Clinic on one or more occasions during the postoperative period. None have been lost to follow-up. The follow-up period of the survivors varied from three and one-half to seven years, averaging four and three-fourths years.

Results have been classified as in the first report. Three categories have been chosen into which postoperative patients surviving operation have been placed for purposes of evaluation. These are (1) excellent, (2) significant improvement, and (3) failure. An operation is considered a failure if the patient did not experience improvement, if the patient died during the follow-up period, if reoperation was necessary, or if significant disability from the residuals of a cerebral embolus remains.

To be considered as having an excellent result, a patient must have resumed almost normal activities. A patient in Class IV (New York Heart Association classification), however, who postoperatively is placed in Class II is considered as having an excellent result. A patient who was in Class III preoperatively and who, despite some improvement in exercise tolerance, is only in Class II postoperatively is considered as showing significant improvement. Obviously all patients who are in Class I postoperatively are considered to have an excellent result.

An attempt has been made to analyze the cause of late deaths and other failures. The incidence of postoperative embolization is also recorded. Other authors have shown little correlation of postoperative heart murmurs, electrocardiographic changes, and roentgenographic appearance of the thorax with the clinical status of the patient.[3,4] It has been shown, for instance, that the postoperative cardiac silhouette remains unchanged in about one-half of the cases, enlarges in one-fourth, and decreases in size in one-fourth.[10] For this reason these factors were not evaluated in the present study.

In the initial report postoperative hemodynamic data were presented on some of the patients. In general these data reflected the clinical status of the patient. Although studies have been carried out on some of the patients reported on here in the late follow-up period, the interpretation of the findings and the implications thereof do not differ sufficiently from those of the original studies to warrant inclusion here.

Clinical Results

A total of 79 patients (65.8%) had an excellent result, while eight patients (6.7%) were considered to be significantly improved (Table 2). Thus 72.5% of patients surviving operation received some benefit, while 27.5% (33 patients) represented failures. When the 11 hospital deaths are included, operation was of benefit to 66.4% of the patients operated on.

For purposes of comparison, the early and late results are shown in Table 3. The two groups are not entirely comparable because of the slightly larger number of patients in the late follow-up group. It is quite obvious that patients with an initial excellent result maintain their improvement. The slightly higher figure in the late follow-up period is merely a reflection of the larger number of patients followed in this group. There is a significant drop in the percentage of patients classified as having significant improvement, with a corresponding rise in the percentage representing late deaths and unimproved patients. Thus, whereas the

TABLE 2.—*Mitral Stenosis—Late Clinical Results in Patients Surviving Mitral Commissurotomy* *

Preoperative New York Heart Association Classification	Patients	Result, Number of Patients				
				Failure		
		Excellent	Significant Improvement	Late Death	Unimproved	Cerebral Residual
I	2	2	—	—	—	—
II	24	19	—	1	4	—
III	64	39	6	8	9	2
IV	30	19	2	7	2	—
Total	120	79 (65.8%)	8 (6.7%)	16 (13.3%)	15 (12.5%)	2 (1.7%)

* Follow-up periods ranged from 3½ to 7 yr.

TABLE 3.—*Mitral Stenosis—Comparison of Early and Late Results (in Percentages of Total Patients)*

Result	Early, %	Late, %
Excellent	62.8	65.8
Significant improvement	24.4	6.7
Failure	12.8	27.5
Late death	7.4	13.3
Unimproved	3.2	12.5
Cerebral residual	2.2	1.7

early results would indicate that 87.2% of patients who survive operation are benefited, longer follow-up of these and other patients reveals that only 72.5% experience improvement. In other words, when the follow-up is for three and one-half to seven years, as compared with a follow-up of three months to three years, there is an increase in the failure rate by a figure of 14.7%.

The early and late postoperative functional status of all the surviving patients not incapacitated by a cerebral embolus is shown in the Figure. More than three-fourths of the patients were in Class III and IV preoperatively. Again the total numbers are not entirely comparable; so the findings are represented as a percentage of the group under consideration. The findings indicate that the percentage of patients in Class I in the early postoperative period remains approximately the same when reevaluated at the late follow-up period. The slight increase in percentage in this later group reflects the increased numbers of patients followed rather than an actual improvement in the status of some patients after a longer follow-up period. Many patients described continued subjective improvement even after the first postoperative year. In each of these cases, however, the predominant functional improvement was evident soon after operation. Further clinical improvement was never sufficient to permit a more favorable functional classification at the later follow-up period. On the other hand, there are a smaller percentage of patients in Class II and a larger percentage in Class III in the later group, as compared to the earlier group. The percentage of patients in Class IV does not differ significantly between the early and late follow-up groups. The lack of increase in Class IV patients in the late follow-up group is probably attributable to the fact that most patients who might have fallen into this class died before completion of the follow-up study.

Causes of Late Death.—There were 16 late deaths in the series, an incidence of 12.2%. When the operative deaths are also considered, the over-all mortality rate for the 131 patients who underwent commissurotomy was 20.6%. Detailed information was not always available as to the cause of these deaths, although we had a report of the postmortem examination in some instances. Eight of the sixteen deaths were considered to be due to cardiac failure. The condition of these patients never improved after operation, and they suffered a gradual downhill course with progressive heart failure. Either an incomplete operation or an advanced stage of the disease with an immobile valve and possibly a low myocardial reserve was considered to be the reason for these late deaths. One patient died following removal elsewhere of an embolus to the aortic bifurcation, and one died of progressive heart failure after a one-and-one-half-year period of striking clinical improvement. The latter patient probably represents an instance of re-

TABLE 4.—*Mitral Stenosis—Factors Involved in Results (in Percentages of 120 Patients)*

	Functional Classification		Age, Yr.		Rhythm		Status of Value	
	Class III & IV	Class I & II	40+	<40	Atrial Fibr.	Reg. Sinus Rhythm	Immobile, Regurgitation, or Both	Pliable & Competent
Success	70.2	80.8	65.9	77.6	62.2	77.1	52.5	82.5
Failure	29.8	19.2	34.1	22.4	37.8	22.9	47.5	17.5

stenosis. The cause of death in six patients was unknown. Four of these patients died suddenly after a variable period of clinical improvement following operation. An arrhythmia, an unsuspected cerebral embolus, or a pulmonary embolus might have played a role in these deaths.

Recurrent Mitral Stenosis.—The problem of recurrent mitral stenosis has received considerable attention in recent years in the literature. Some reports maintain that restenosis does not occur,[11] while on the other hand increasing numbers of apparently definite cases of this sort are being reported.[12] We believe that a patient must have demonstrated an initial definite period of functional improvement after operation, for at least six months and preferably a year or more, before a diagnosis of restenosis can be made.

On this basis, 1 of the late deaths and 9 of the 15 unsatisfactory results were considered as possible examples of restenosis, an incidence of 8.3%. The discrepancy between this figure and the figure of 14.7%, which represents the increased rate of failure in the late follow-up period, as compared to the early results, needs explanation. Patients who were initially classified as improved but not as having an excellent result were usually unimproved when reevaluated at a later date. They never were strikingly improved and hence were not considered examples of restenosis. In retrospect their early favorable classification was of short duration only and probably not truly indicative of any beneficial effects from the operation. The remainder of the 15 patients who failed to benefit from the operation were actually unimproved by the operation at any time, and again they represent either an advanced stage of the disease or an incomplete operation. We are firmly convinced that a thorough enlargement of the mitral orifice must be obtained to prevent poor results. We agree with Bailey and associates [13] that in the majority of cases the use of a cutting instrument is necessary and that both commissures should be incised out to the valve ring if indicated and the leaflets mobilized to achieve this. Many cases of so-called restenosis are unquestionable instances of incomplete operation.

Among the 10 patients in whom restenosis of the valve apparently developed, two factors seemed of prime importance. An immobile valve was present, in five patients. In two a history suggestive of acute rheumatic fever occurred in the postoperative period. The latter development emphasizes the importance of a prophylactic antibiotic regimen postoperatively in appropriate cases. Three patients in whom the mitral valve was pliable at operation and in whom an excellent opening was obtained at operation had initial excellent results, but later their condition deteriorated for no obvious reason.

The time of onset of recurrent symptoms in these 10 patients thought to have had recurrent mitral stenosis ranged from eight months to five years, averaging two years nine months after operation. The fact that restenosis can occur as long as five years after operation indicates the necessity for continued close follow-up of patients who undergo mitral commissurotomy.

Six of the patients with restenosis were operated on a second time, five by us and one at another institution.* Three of these patients are now definitely improved again; one is unimproved; one died after reoperation, and one died subsequently. The follow-up period is brief and the numbers of patients small. However, the fact that the condition of 50% of these patients was improved supports the advisability of reoperation when indicated.

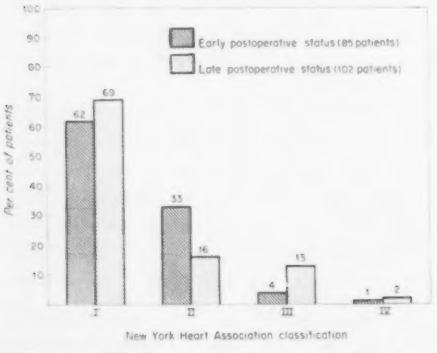
Postoperative Embolization.—Peripheral arterial embolization is one of the risks to which a patient with mitral stenosis is subjected, and a decrease in this risk postoperatively would indicate that the operation affords the patient some protection. Most reports would indicate that postoperative

*Dr. Benson Roe, of the University of California School of Medicine, San Francisco, reoperated on this patient and provided us with the follow-up information.

emboli, exclusive of those occurring at the time of operation, are rare. Among the 120 patients who survived operation, there occurred 4 known cases of arterial embolization, an incidence of 3.3%. Fifteen (12.5%) of the 120 patients had experienced embolization one or more times before operation. There were, then, about four times as many patients who experienced arterial embolization before operation as afterward. Two of the four patients suffered embolization in the legs. Neither lost his limb. There were two emboli to the aortic bifurcation, and, as already noted, one of these patients died. Only one of the four patients had experienced embolization before operation. The remaining 14 patients with a history of preoperative emboli have remained free of embolization.

Factors Involved in Results

A variety of factors may be considered as influencing the long-term results in patients who undergo mitral commissurotomy. We have chosen to evaluate the following: (1) the initial functional classification of the patient, (2) the age of the patient, (3) the cardiac rhythm, and (4) the mobility of the valve and associated regurgitation (Table 4). In this early group of patients only a few had associated disease of other valves. This factor, which certainly can affect end-results, was not influential in this group of patients. Evaluation of the status of the myocardium as a determining factor seemed too uncertain to warrant inclusion. Indirectly the status of the myocardium probably plays a role in influencing the subsequent course of patients with a poor functional classification. Since the surgeon's impression of the size of the postcommissurotomy orifice does not lend itself well to accurate measurement, this factor was not considered. As has been pointed out, it is our opinion that a complete opening is essential in order to achieve the best results. To accomplish this, mere fracture with the finger is seldom adequate.



Early and late postoperative status of patients surviving mitral commissurotomy.

Functional Classification.—The results in the Class III and IV patients were compared with those in Class I and II. There was no difference between the results in Class IV patients and those in Class III patients. The findings are as follows: Whereas 29.8% of the operations failed in Class III and IV patients, only 19.2% failed in Class I and II. This indicates a slightly better prognosis for patients who are operated on before their disease has progressed to the point of severe functional disability. The known high operative mortality rate in Class IV patients adds to the significance of these figures.

Age.—When the results are calculated for patients less than 40 years of age and for those 40 or more years of age, a slight advantage for the patients in the younger age group is noted; 77.6% of patients in the younger group were benefited by operation, whereas 65.9% of those in the older group were benefited.

Cardiac Rhythm.—Auricular fibrillation usually connotes a more advanced form of the disease and might be expected to influence the end-results. Some evidence for this was found, for failures occurred in 37.8% of patients with auricular fibrillation, whereas only 22.9% of the procedures failed when sinus rhythm was present.

Status of Valve.—The results were further analyzed in relation to the status of the valve as found by the surgeon at the time of operation. The presence of immo-

bility of the valve associated in many instances with calcification, which cannot always be recognized roentgenologically, and the presence of preoperative regurgitation graded as 2 or more (on the basis of 1 to 4) were considered as possible adverse valvular characteristics. Regurgitation of any significance was not often found in the presence of a pliable valve in this group of patients with predominant mitral stenosis. The results in these cases were compared with the results in patients with pliable competent valves. The operation failed in 47.5% of patients whose valves were immobile or incompetent or both, as opposed to 17.5% in patients with pliable competent valves. When one considers the fact that all 11 patients who failed to survive operation had immobile valves, most of them incompetent, the significance of this adverse factor can be further appreciated.

The surgical production of mitral insufficiency was investigated as a possible cause of a poor postoperative result. Although a slight amount of regurgitation may be produced surgically or preexisting regurgitation may be increased, no postoperative death could be attributed to this factor. The failure of one patient to improve after operation was considered to be due in part to the surgical production of mitral insufficiency.

As seen in Table 4, all of the factors considered had some influence on the surgical result. The status of the mitral valve shows the most striking relationship. Whereas functional classification, age of the patient, and cardiac rhythm, when considered separately, influenced results by a factor only 10% to 15%, patients with pliable competent valves had a 30% higher rate of success than patients with immobile or incompetent valves or both. This factor stands out as the most significant one in the late follow-up group, as it did in the early follow-up group.

Comment

There is already ample evidence that mitral commissurotomy, although a palliative operation, favorably affects the prognosis of patients with mitral stenosis.[3] Our results are much in keeping in this regard with others that have been reported.

In analyzing the significance of the results reported here, it must be emphasized that they represent the first group of mitral commissurotomies carried out at our institution. Unquestionably some of these patients did not have the benefit of as complete a commissurotomy as is now performed. Whereas it is our present practice to open the posteromedial commissure whenever indicated, this commissure was rarely if ever incised in this first group of patients. In spite of the fact that many of these patients had an incomplete operation by present standards, the over-all sustained improvement rate of 72.5% of surviving patients is gratifying. When compared with the early results after operation, this indicates a 14.7% increased rate of failure as the follow-up period is lengthened. One might anticipate a lower rate of failure with a more extensive operation, particularly in patients with a pliable competent valve.

Analysis of various factors affecting the results of operation indicates that the functional status of the patient, his age, the cardiac rhythm, and the anatomic status of the valve all play a role. The presence of an immobile valve with or without regurgitation or the presence of significant preoperative regurgitation has the most serious prognostic significance of any of the factors mentioned. Unfortunately the immobility of the valve cannot always be anticipated prior to operation, particularly in the absence of roentgenographic evidence of calcification.

How should these findings influence our present and continued management of patients with mitral stenosis? Since it is a palliative procedure, it should be carried out only on patients who are in need of help from a symptomatic standpoint. The importance of accomplishing as complete an opening of the mitral orifice as possible has already been adequately emphasized. Early operation, done when the patient is young and before the development of serious func-

tional disability, auricular fibrillation, or immobility of the mitral valve, is clearly indicated. An excellent long-term result should be anticipated in a high percentage of such patients when operated on by the classic closed method of mitral commissurotomy.

In the presence of immobility and regurgitation of the mitral valve, good results may still be obtained in about half of the patients surviving mitral commissurotomy. Obviously, therefore, they should not be denied operation even though the results are less favorable and the operative risk is greater. It is in this group of patients that open operation with use of extracorporeal circulation might be considered. Although good initial results in the treatment of patients with relatively pure mitral insufficiency have been obtained at our institution by open operation,[14] we have had no experience with the combined lesions of stenosis and insufficiency. It is difficult to visualize a satisfactory operative procedure which might restore function to a narrow, rigid, distorted, calcified, and partially incompetent mitral valve, short of replacement with a prosthesis. For this reason we have been reluctant to consider open operation in these cases in the absence of a suitable prosthetic valve. Although a satisfactory result might be achieved in rare instances, we prefer to continue the use of closed mitral commissurotomy as a palliative procedure in such cases until better techniques are available.

Summary

Early postoperative results on the first 131 patients to undergo mitral commissurotomy at the Mayo Clinic were reported previously. Further follow-up studies have been made on the 120 patients who survived the postoperative period in the hospital. None has been lost to follow-up. The postoperative period of observation varied from three and one-half to seven years, averaging four and three-fourths years.

Of the 120 survivors, 72.5% either maintained an excellent result or continued to be significantly improved by the operation, while 27.5% represented failures. Including the operative mortality, then, the operation was of benefit to 66.4% of the total original group. In the group of late failures 12.5% of the patients were unimproved and 13.3% died. The over-all mortality rate including hospital deaths was 20.6%.

Restenosis of the mitral valve was considered to have occurred in 10 patients (8.3%). Six of these patients have been reoperated on, and three of these have been improved following the second operation. Arterial embolization occurred in four patients during the follow-up period. This incidence of arterial embolization is one-fourth the preoperative incidence.

Analysis of the various factors affecting the results of operation indicates that the functional status of the patient, his age, and the cardiac rhythm all play a role. However, the anatomic status of the valve itself was the most significant factor in determining the postoperative result. The presence of an immobile valve with or without regurgitation or the presence of significant preoperative regurgitation alone led to a poor result in 47.5% of such cases, whereas failure occurred in only 17.5% of the group of patients with pliable competent valves.

The necessity of achieving a complete opening of the valve is stressed. Many of these early patients did not have a complete operation by our present standards. Early operation before the development of the various adverse factors is advisable. A high percentage of good results at a low operative risk should be achieved in such patients by mitral commissurotomy.

Although the results are poorer and the risk higher in patients with a calcified immobile valve with associated regurgitation, many such patients will be benefited by commissurotomy. When better techniques have been developed, particularly when a satisfactory prosthetic replacement for the mitral valve is available, such patients may become candidates for open-heart repair with use of extracorporeal circulation.

Mayo Clinc.

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Clinical and Laboratory Features of Malignant Carcinoid

ALBERT SJOERDSMA, M.D., Ph.D., Bethesda, Md.

It is only a few years since Thorson [1] and others recognized the association of several unusual signs and symptoms with carcinoid tumors of the small bowel with hepatic metastases. It is apparent now that (1) carcinoid (argentaffinoma) is an endocrine tumor which produces the pharmacologically active agent, serotonin (5-hydroxytryptamine), and (2) the various manifestations of the "carcinoid syndrome" are attributable to secretion of serotonin by the tumors and a disturbance in the metabolism of tryptophan.[2] Since many cases of the disorder have now been recognized,[3,4] both the general practitioner and the specialist should be aware of this condition and become acquainted with the simple chemical test [5] on urine by which it may be diagnosed.

Clinical Features

A series of baffling illnesses extending over a period of years is typical, coinciding with slow growth of the tumor. Current clinical concepts are derived chiefly from study of advanced cases. The clinical features may be listed as follows.

Vasomotor.—The commonest and often the earliest manifestation is paroxysmal erythematous flushing of the face and neck, with variable involvement of other skin areas. Remarkable changes in color may appear within a few minutes, ranging from bright red to violaceous to blanching-white. Facial and periorbital edema, tachycardia, hypotension, and increased respiratory and intestinal distress may occur with severe flushing. Precipitating stimuli include emotional upsets, defecation, physical activity, and manipulation of the tumors. After several years, miliary and gross telangiectasia may develop and give an appearance of cyanosis in the absence of arterial O_2 desaturation.

Gastrointestinal.—There is usually a long history of abdominal discomfort in association with recurrent attacks of diarrhea. Nausea and vomiting develop in the presence of frequent or prolonged flushing. Hyperperistalsis is often apparent at the bedside. Although the primary tumor is usually silent, hepatic metastases frequently undergo necrosis, leading to episodes of pain in the right upper quadrant of the abdomen, with fever and leukocytosis. Hepatomegaly may become massive, but hepatic function as measured by the usual tests is often well preserved and alterations in the tests are nonspecific. An increased incidence of peptic ulcer has been noted.

Cardiopulmonary.—Cardiac involvement is a late manifestation and occurs in about 50% of far-advanced cases. Right heart failure may supervene in association with pulmonary and tricuspid valve lesions. However, dependent edema is common even in the absence of cardiac disease. Clinical and laboratory findings relating to the heart are comparable to those seen in similar valvular lesions of rheumatic or congenital origin and vary with the severity of involvement. Some patients have attacks of dyspnea and wheezing indistinguishable from bronchial asthma. Others experience constricting sen-

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sations in the chest and recurrent paroxysms of coughing.

Nutritional.—Loss of weight occurs intermittently but is progressive. Cutaneous lesions of pellagra have been encountered in several cases, and hypoalbuminemia is a frequent finding.

Laboratory Features

Pathological.—Malignant carcinoid usually develops from a small primary lesion of the ileum. Hepatic metastases are found in advanced cases, and ovarian metastases are frequent in the female. More distant metastasis may occur, particularly to lung and bone. The tumors are yellow in color and firm on section and consist of epithelial cells set in a fibrous stroma. Intracellular granules giving the chromaffin-argentaffin reactions reflect presumed origin of the tumor from the enterochromaffin cells of the intestinal mucosa.

Associated pathology is found primarily in the skin and right side of the heart. Greatly dilated capillaries and veins are seen in the skin, representing telangiectasia during life. Fibrosis of the right atrial and ventricular endocardium may involve the valve leaflets and chordae tendinae to produce pulmonic stenosis, tricuspid stenosis, and tricuspid insufficiency, alone or in combination. Cardiac involvement has not been observed in the absence of hepatic metastasis.

Biochemical.—The major depot of serotonin in the body is the gastrointestinal mucosa. Smaller amounts are found also in the brain and blood platelets. This amine is derived from the essential amino acid, tryptophan, and is metabolized to 5-hydroxyindoleacetic acid (5HIAA), which is excreted in the urine (tryptophan→5-hydroxytryptophan→serotonin→5HIAA). In patients with malignant carcinoid, the tumor is the major body depot of serotonin and generally contains 1-3 mg. per gram. Blood levels of serotonin are elevated to 0.5-3.0μg. per milliliter, compared to normal values of 0.1-0.3μg., and the urinary secretion of 5HIAA is greatly elevated, usually being 50-600 mg. per day, compared to 2-10 mg. per day in normals. As much as 60% of dietary tryptophan may be deviated into the serotonin pathway by the tumor, whereas normally only about 1% is metabolized in this manner. This diversion of tryptophan leaves less available for the formation of other substances, such as nicotinic acid (niacin) and protein.

Clinical-Biochemical Correlations

The pharmacologic effects of serotonin on smooth muscle account for the vasomotor disturbances, hyperperistalsis, and bronchoconstriction. The acquired lesions of the right heart are probably also on a chemical basis but have not been produced experimentally. Because of the abnormality of tryptophan metabolism in patients with malignant carcinoid, decreased food intake and loss of nutrients by diarrhea which would not significantly affect a normal person may lead to the development of pellagra and protein deficiency.

Further clinical and chemical studies will be required to ascertain whether carcinoid tumors arising in the colon, stomach, or bronchi (adenomas) may produce serotonin and the typical syndrome.

Diagnosis

The syndrome is recognized readily when it is fully manifest. However, it is important to realize that any single sign or symptom may be the sole or predominant evidence of functioning carcinoid. The primary tumor usually cannot be visualized by intestinal roentgenography. Needle biopsy of the liver may be helpful but is often inconclusive. The diagnosis is established easily by a simple qualitative test[5] of the urine for an elevated excretion of 5HIAA. A more detailed quantitative procedure is necessary to measure amounts less than 30 mg. per day. Values above 15 mg. per day are sufficiently high to indicate a diagnosis of carcinoid. Certain precautions must be exercised in carrying out the chemical tests.

Urine should be collected at a time when no medications are being administered, and one should make certain that the patient has not ingested bananas. Urinary metabolites of phenothiazine drugs such as chlorpromazine caused quenching of the color reaction and may produce a false-negative test.[6] Only a distinct purple color constitutes a positive test; a red or pink color such as follows the ingestion of certain drugs (e. g., Robitussin [expectorant and antitussive containing glyceryl guaiacolate and deoxyephedrine hydrochloride] and mephenesin [Tolserol]) is negative. Recent studies[7] have shown that bananas contain large amounts of serotonin, about 4 mg. per average banana pulp. Since serotonin administered orally is almost entirely metabolized to 5HIAA, ingestion of a few bananas will produce a "true" false-positive test.

Therapy

Because of the slow growth of both primary and metastatic carcinoid tumors, radical surgical extirpation is indicated even when the tumors cannot be removed completely. In this regard, serial measurements of urinary 5HIAA are of unique value in judging the effectiveness of surgery and the course of subsequent tumor growth. Even if they are asymptomatic, localized, and mildly invasive, carcinoid tumors should be removed promptly because of their malignant propensities. Since the primary tumor of the malignant carcinoid occurs most frequently in the lower ileum, it is advisable to inspect and palpate the lower ileum during routine abdominal surgery, and if "benign" lesions are recognized, prophylactic excision is believed justified.

Medical therapy, including irradiation, is generally unsatisfactory. With the possible exception of chlorpromazine, the so-called serotonin antagonists currently available have been ineffective. An adequate diet and vitamin supplements, including nicotinic acid, seem indicated. Other measures are nonspecific and constitute the treatment of symptoms and complications. Treatment of heart failure is the same as that for failure from other causes. A prompt means of diagnosis, plus knowledge of the chemical alterations induced by the tumor, should lead to more effective therapy of this disorder.

Conclusions

Clinical and laboratory findings in patients with malignant carcinoid are reviewed. Chemical tests on the urine for elevated excretion of 5-hydroxyindoleacetic (5HIAA) should be done in all cases of unexplained diarrhea and visible flushing. It is felt that in this way some patients will be recognized to have this disorder at a stage when surgical intervention will result not only in palliation but also cure.

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Relationships Between Cancer and Viruses

WENDELL M. STANLEY, Ph.D., Berkeley, Calif.

The first direct causal relationship between cancer and a virus was established experimentally in 1908 by Ellermann and Bang in their work on the transmission of fowl leukemia by means of cell-free preparations. Unfortunately, this important experiment failed to have the impact on contemporary investigations that it should have because the neoplastic nature of this disease was not then clearly recognized. However, shortly thereafter, in 1911, Peyton Rous found that a sarcoma that appeared spontaneously in a Plymouth Rock chicken could be passed from chicken to chicken by means of cell-free filtrates. Clearly, here was a malignant growth caused by a virus or virus-like agent. Although for a few years some doubt regarding the true relationship between the virus and the sarcoma existed, the Rous virus did serve to set the pattern, and today tumor viruses of chickens and other avian species are accepted without question. In addition, the situation with respect to fowl leukemia has been clarified somewhat, although areas of uncertainty still remain. Beard and associates have concentrated and purified two distinct leukemia viruses. Burmester has secured evidence which indicates that lymphomatosis is characterized by a group of related viruses. It is possible that all or most of the avian leukemia and tumor viruses, including the Rous virus, may be related more or less closely.

In 1932, Shope found a fibroma of rabbits which was caused by a virus. Later on, Berry and Dedrick reported that inoculation of a mixture of heat-inactivated myxoma virus and active fibroma virus resulted in myxomatosis. This very interesting situation is still greatly in need of further experimentation. In 1940, Duran-Reynals noted that inoculation of newborn rabbits with small doses of fibroma virus caused tumors or generalized fibromas, whereas larger doses of the same virus caused necrotic inflammatory lesions not too different from those caused by myxoma virus. This work was the forerunner of much important later work of a similar nature with still other viruses by Duran-Reynals.

In 1933, Shope discovered in our native wild cottontail rabbit the now famous papilloma virus of rabbits. This virus causes a benign tumor or papilloma in the wild rabbit which only occasionally develops into a malignant growth with metastases. However, inoculation into domestic rabbits is followed by the development of papillomas which, unlike those in wild rabbits, appear to contain no infectious virus and which almost always progress into cancers, and in these there still seems to be no infectious virus. Immunological evidence for the existence of virus in the domestic rabbit papillomas and cancers has been obtained by Rogers, Kidd, and Rous. Furthermore, Rous and Friedewald have found that the cancers derived from papilloma-virus-infected rabbit cells on treatment with chemical carcinogens or tar were of the same type that arise from these cells spontaneously after a much longer time. This work would seem to indicate that the chemical carcinogens acted by way of the virus. The rabbit papilloma virus has been concentrated and purified, and many of its biochemical and biophysical properties have been studied.

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Professor of Virology and Biochemistry and Director of the Virus Laboratory, University of California.

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Needless to say, the unusual opportunity which is provided by this system to study the transition from a benign virus-induced papilloma to a malignant growth has been and is still being extensively investigated. During recent years papillomas of the skin and oral mucosa of several different animals, such as horses, cows, cats, dogs, and rats, have been found to be transmissible by means of filtrates. Unfortunately, these have been little studied; hence, the extent as well as the importance of these viruses remains in doubt. A recently reported very interesting virus is one discovered in 1955 by Shope, which causes fibromas in deer.

In 1934, Lucké reported the isolation of a filterable agent from an adenocarcinoma of the leopard frog. It is of some interest that inoculation of this virus into distant sites of the leopard frog yielded no local tumors but did yield kidney carcinomas and that inoculation into other kinds of frogs yielded no tumors. This example of high specificity of a cancer virus is one that should be kept in mind. In 1936, Bittner discovered the agent in the milk of mice which seems to be responsible for the development of breast cancer in mice many months after inoculation of the agent. However, genetic and hormonal factors have been found to play an exceedingly important role, so much so that some situations are known in which breast cancer is present without demonstrable virus and in other situations virus can be inoculated without the subsequent appearance of breast cancer. While there is no doubt with respect to the existence of a virus that can cause breast cancer in mice under specified conditions, our knowledge of the interplay between viral, genetic, and hormonal factors leaves much to be desired. DeOme and his associates are presently doing much to elucidate these factors. Here is an area of research which, if properly exploited, could lead to knowledge of supreme importance to the human cancer problem.

Black, in 1945, described a leafhopper-transmitted virus that would cause tumors on the roots of sweet clover plants as well as in many other plants. The tumors caused by this wound-tumor virus were found to differ from the outgrowths known earlier in certain tobacco and sugar cane diseases in that they seemed capable of indefinite growth as unorganized tissue. Black has pointed out that striking similarities exist between the wound-tumor disease and mammary cancer in mice in that a virus plays an important role in each but that genetic and hormonal factors can have a tremendous influence on the virus-host reaction.

In 1951, Gross reported that the inoculation into newborn mice of strains free of leukemia with cell-free filtrates of extracts of leukemic organs from mice of a high leukemic strain resulted in leukemia within one or two years. Stewart, Eddy, and Law, at the National Institutes of Health, and several other investigators have devoted much time and effort to studies of this mouse leukemia, and it now appears likely that several viruses causing different kinds of tumors are actually involved and that the genetic factors and age of the host as well as the nature of the host itself play a much more important role than suspected earlier. The separation and recognition of the different viruses or virus strains and their corresponding diseases and the elucidation of the role played by genetic factors represent problems of the first magnitude. However, today there seems to be no doubt but that these mouse viruses can cause cancer, and this is, of course, the important fact for the present discussion.

Friend has recently reported the discovery of a filterable agent which will induce leukemia in mice of any age as soon as two or three weeks after inoculation. This remarkable agent was found during the course of studies on the effect of cell-free preparations of the Ehrlich ascites tumor in infant Swiss mice. Since infant mice are not necessary and because of the rapidity with which the disease develops, this virus would appear to possess definite advantages for exploratory experimentation over the viruses which Gross has investigated. Friend has already

demonstrated that a formalinized vaccine made from the virus can confer a substantial degree of protection against leukemia.

This very brief review of cases in which there is good experimental proof for a direct causal relationship between viruses and cancer in animals and plants should be sufficient to secure acceptance of the fact that viruses can cause cancer. It is necessary next to appreciate that basic biological phenomena generally do not differ strikingly as one goes from one species to another and, hence, that the fact, now proved beyond contention, that viruses can cause cancer in animals is directly pertinent to the human cancer problem. Recent advances in the cultivation of human cells in vitro and especially the newer knowledge of certain properties of viruses warrant today a marked change in our thinking on the problem of human cancer. The time has come when we should assume that viruses are responsible for most kinds of cancer and design and execute our experiments accordingly. Cancer is basically a problem in growth, and there is no reason to believe that the growth of most human cells is different basically from the growth of most animal cells. Acceptance of the viral etiology of human cancer as a working hypothesis will involve a marked change in attitude on the part of many investigators, but this is necessary if the right approach and the right design of experimentation are to result. What we do depends in large measure upon what we think.

Since there is no experimental evidence that human cancer is infectious, many investigators believe that because viruses are infectious agents they cannot possibly be of etiological importance in human cancer. However, this is not a valid conclusion, because it is well known that animal tumor viruses may alternately be filterable and infectious and then nonfilterable and noninfectious, owing apparently to variations in the amount of virus present and the fact that viruses may be highly specific, so specific, in fact, that a given virus will infect and cause disease only in one kind of cell in one kind of animal and, hence, under many conditions appear noninfectious. Inoculation into the mucous membrane of a susceptible rabbit of the Shope rabbit papilloma virus yields no tumors. Under these conditions this virus would appear to be noninfectious. Even the Rous sarcoma virus when first isolated would cause cancer only in blood relatives of the chicken from which it was obtained. Later on this virus was adapted to other chickens and to other types of fowl, such as ducks and pheasants. In some cases this involved several passages in the new host by means of cells before it became possible to pass the tumor by means of cell-free filtrates. In order to transmit a virus from a given host to a more distantly related host it is usually necessary to adapt first to an intermediate host. Normally, one would not expect that a virus, long adapted to existence in human cells, would go readily in most animal cells. However, the fact that some human viruses have been found to grow in certain animal cells indicates that the situation is not completely hopeless and, hence, that the search should continue. Nevertheless, it should be obvious that great difficulties might be involved in demonstrating the existence of a virus that is actually present in a human cancer. Until these techniques have been used exhaustively without success, it would be foolish to disregard the role which viruses may be playing in human cancer.

Needless to say, the cultivation of human cells in vitro opens up wonderful experimental possibilities. The work of Earle on tissue cultures and Gey and associates on HeLa cells has stimulated much activity in the cultivation of human cells. We have, in our own laboratory, about a dozen different kinds of normal and malignant cells of human origin under cultivation. While most of these are being used for studies on the effects of known viruses, it is obvious that such cells can be examined for the presence of hitherto unknown, as well as known, viruses or can be used as test ma-

terials for suspected human viruses. The human amnion cell, which my colleagues, Zitcer, Fogh, and Dunnebacke, first obtained from the full-term amnion in cell culture, is proving of great use in this connection as well as in studies on the transition from a normal to a potentially malignant cell. For example, we are finding interesting changes in chromosome number and in ability to grow in cortisone- or x-ray-treated animals as these human amnion cells are passed in culture. Many other laboratories have normal and malignant human cells under cultivation, and significant new findings may be expected to result from this new and potentially extremely powerful experimental approach.

Another fact of importance, first recognized with the Rous sarcoma virus, is that a given tumor may be transmissible for a time only by the inoculation of living cells and later be transmissible by means of cell-free filtrates. The fact that this occurred with the Rous sarcoma was used as an argument against the viral causation of this tumor for a long time. However, similar results were obtained in the case of other tumors, and it was thought that the variation in transmissibility was due to differences in the actual amount of virus produced. Recently, Carr and Duran-Reynals proved experimentally that the amount of virus present in the tumor tissue is dependent upon the age of the host and the age of the tumor; in general, the younger the host and the younger the tumor, the more virus that can be extracted. However, it should be noted that Duran-Reynals found that inoculation of Rous virus to newly hatched chicks results in a hemorrhagic, rather than a neoplastic, response. Bryan and co-workers made a thorough study of the relationship between the amount of Rous virus inoculated and the amount of virus extractable from the tumors at different times. It was found that the extractable virus approached a maximum when relatively strong inocula were used but that at lower dosage levels the amount was highly correlated with the dose. They also found that very small doses of virus yielded tumors from which no virus was recoverable by extraction. Rubin is studying the Rous virus in tissue culture and has obtained important new information concerning the propagation of the virus.

Beard has assembled evidence that differences in the infectivity of Shope virus papillomas of wild cottontail and of domestic rabbits, generally ascribed to latency or masking in the latter, are due not to differences in the nature of the virus but to wide differences in the actual amount of virus present in the papillomas. The rate of virus production within cells may vary greatly so that in some cases hundreds to hundreds of thousands of virus particles are produced per cell, whereas in other cases the rate of virus production may approach or may be the same as the rate of cell division. In the former case, the diseased tissue or tumor would be expected to yield large quantities of virus and hence represent a highly infectious situation, whereas in the latter case, the diseased tissue or tumor might be regarded as noninfectious because of the lack of demonstrable virus. Changes in nutrient or in temperature during the period of virus growth can cause drastic changes in the amount of a virus present in a host. It is obvious, therefore, that before one should conclude that a given tumor is nonviral in nature, one should be certain that the extract has been tested on cells known to be susceptible and to yield a demonstrable reaction with the virus and that the virus is absent, in fact, and not just present in provocative, yet subinfectious, amounts. Needless to say, it is well known that proper concentration procedures may convert subinfectious preparations into infectious preparations.

One sometimes hears the argument that cancer viruses do not exist in human beings, because if they did exist, someone would have found them by this time. Some attention might have been given to this argument some years ago, but not now, for

literally dozens of hitherto unknown human viruses have been discovered during the past few years. Extracts of stools were used to inoculate monkey kidney and occasionally other cells in tissue culture and this resulted in the discovery of dozens of enteric viruses known as the ECHO viruses. Another group, consisting of many viruses isolated in a similar fashion but from the upper respiratory tract of man, is known as the APC or ARD viruses or, more recently, as the adenoviruses. Still a third group of viruses has been isolated from samples of human sera. Thus we have today many more human viruses than we know what to do with; hence, there is now certainly no reason to shy away from giving consideration to viruses as causative agents in cancer for lack of the viruses. Actually, these recent developments lead one to suspect that there are many more undiscovered viruses present in presumably normal human beings.

The finding that the APC viruses had a cytopathogenic effect on a human cancer cell, the HeLa cell, suggested to Huebner and other scientists at the National Institutes of Health that these viruses might have some effect on similar cells in human beings. It was found that the injection of these viruses into a cervical cancer mass or into the blood stream resulted in the disintegration and disappearance of most of the cancerous mass. However, all of the cancer cells were not destroyed by the time that neutralizing antibodies to the virus developed, and these served to protect this residual cancer. Earlier work, by Southam and Moore, had shown that the inoculation of human beings carrying a cancer with certain neurotropic viruses sometimes caused regression of the cancer. Work of this general nature is just in its infancy, but the fact that infection of certain cancer cells with certain viruses causes the destruction of the cancer cells is most significant. Because of the well-known plasticity of viruses it should be possible, by means of already known passage techniques, to develop viruses having no obvious effect on normal cells but with a special predilection for the destruction of cancer cells. Several laboratories are already engaged in work of this type.

It has long been known that cancer could result from prolonged exposure to coal tar, and since 1920 extensive studies on chemical carcinogens have been made. It has generally been assumed that the carcinogen has caused some change in a cell which then progresses to cancer, but a few investigators have suggested that the chemical carcinogen works by activating or by causing a mutation in a latent virus. Rous and Friedewald have made extensive studies on the effect of chemical carcinogens on virus-induced rabbit papillomas, and their evidence would seem to indicate that the chemical carcinogens acted by way of the virus. Duran-Reynals found that, in practically every case, treatment of chicks, adult chickens, and pigeons with methylcholanthrene activated a latent or subinfectious fowlpox virus which produced lesions and these subsequently progressed to cancer. His work certainly brings to the forefront the question as to whether or not an ordinary virus like fowlpox can be a potential cancer virus.

In view of the great variety of carcinogens, which range from hundreds of different kinds of chemicals to physical agents such as ultraviolet or x-irradiation and to mechanical effects such as continued abrasions or irritations, the supposition that cancer results from some change within the cell is very reasonable. But if cells have viruses as passengers within them and viruses can cause cancer, it is just as reasonable to assume that these diverse agents are affecting the virus as it is to assume that they are affecting the genetic apparatus of the cell.

The finding of many hitherto unknown viruses in human beings and the possibility that such viruses may persist within the cells of man for years, if not for a lifetime, is really not too surprising. It is well known, for example, that most human beings acquire the virus of herpes simplex very early

in life and, in many persons, the evidence for the persistence of this virus throughout their lifetime is very good. Traub has found that infection of a mouse colony with the virus of lymphocytic choriomeningitis can result, with time, in an inapparent infection of all animals. The virus is apparently transmitted in utero and remains with the animal throughout its life; hence, this virus persists through generation after generation of mice. It is interesting to note that injection of mice from such a colony with sterile broth can revive the pathogenicity of the virus. Karl Meyer has shown that psittacosis virus can persist in the form of an inapparent infection in groups of parrots and certain other birds for long periods of time, only to have frank disease appear following unusually crowded conditions. Shope has shown experimentally that swine influenza virus can remain in a masked or latent form in the intermediate host, the swine lung worm, for very long periods of time. Certain potato viruses, such as potato X-virus, can be passed from generation to generation without causing an apparent disease. The persistence of a virus in man for many years, for a lifetime, or even for two or more generations should not be regarded as an unexpected or unusual phenomenon but rather in complete accord with a well-established biological principle.

The fact that viruses may persist in cells for generations provides ample reason for us to consider the relationships between viruses and genes, since under these conditions both genes and viruses are passed from generation to generation of cells and there is something in the cancer cell which also is passed from cell to cell. Both genes and viruses seem to be nucleoproteins and both reproduce only within specific living cells. Both possess the ability to mutate. Although viruses generally reproduce many times within a given cell, some situations are known in which they appear to reproduce only once with each cell division. Genes usually reproduce once with each cell division, but here also the rate can be changed, as, for example, in the case of polyploidy resulting from treatment with colchicine. Actually the similarities between genes and viruses are so remarkable that viruses very early were referred to as "naked genes," or "genes on the loose." Two discoveries, one which began in 1928 and the other which occurred in 1952, have provided experimental evidence for an exceedingly intimate relationship between viruses and genes. In 1928, Griffith found that he could transform one specific S-type of pneumococcus into another specific S-type by injecting nonvirulent R-forms into mice together with large amounts of heat-killed S-pneumococci of a type other than that of the organisms from which the R-cells were derived. Living virulent S-organisms of the same type as the heat-killed S-forms were then recovered from the animals. Later Dawson and Sia, as well as Alloway, found that the addition of an extract of one type of capsulated pneumococcus to a culture of a noncapsulated rough form would convert the latter into the same type of capsulated pneumococcus which provided the extract. It was obvious that something was being transferred, and in 1938 I discussed the possibility that this "something" might be a virus. In 1944, Avery and his colleagues proved that this something was a transforming principle consisting of deoxyribonucleic acid (DNA). That the phenomenon was not an isolated one was demonstrated in 1953, by Leidy and Alexander, who obtained similar results with an influenza bacteria system. The close relationship to genetics was further emphasized by work of Hotchkiss and by Ephrussi-Taylor who, as well as Leidy and Alexander, showed that drug resistance and other genetic factors could be so transferred. This work provided evidence that genetic factors, or genes, if one prefers such a designation, can be represented by DNA and can be obtained in chemically pure solution.

This information as well as our knowledge of viruses was soon fortified by the very important discovery by Zinder and Lederberg, in 1952, of transduction in Salmonella

by means of a bacterial virus. It was found that genetic factors could be carried from one type of Salmonella cells to another type by means of a bacterial virus. In this type of transformation the genetic fragment is not free but is carried within the structure of the bacterial virus. The closeness of the relationship between the virus and the genes of the host is emphasized by the fact that the transducing ability of any bacterial virus is determined strictly by the character of the cells on which the virus was most recently grown. In transduction, a fragment of a chromosome which might be regarded as a gene or a collection of a few or even many genes can be transferred from one kind of donor cell to another kind of receiver cell and be incorporated into the genetic apparatus of the receiver cell. In the pneumococcus or influenza bacterium this can be caused by a DNA preparation which can be separated and isolated as such, and in Salmonella this gene or gene collection rides within the bacterial virus, presumably with the viral DNA, which is added to the cell to be transduced. Here one hardly knows what to call a virus and what to call a gene, for it is obvious that at times the two merge completely.

I should like to mention a recent very important discovery made in this laboratory by Dr. Fraenkel-Conrat, since this finding may prove very pertinent to a consideration of relationships between viruses and cancer. It was reported by Fraenkel-Conrat and also shortly thereafter by Gierer and Schramm, in Germany, that special treatment of tobacco mosaic virus yielded a nucleic acid preparation possessing virus activity. It would now appear necessary to recognize that a nucleic acid structure perhaps as small as 300,000 in molecular weight can possess coded within its 1000 or so nucleotides not only all of the information that is necessary to bring about in the host cell the production of more of this same nucleic acid but also apparently the *de novo* synthesis of its own characteristic and highly specific protein with which it eventually coats itself. This work provides wonderful evidence for a direct relationship between specific nucleic acid and specific protein synthesis and makes it possible to consider virus and gene action, including their relationships to cancer in terms not of nucleoprotein structure but in terms of nucleic acid structure.

Now, of course, there are direct approaches to the human cancer problem which should be continued and even intensified in view of several interesting experimental results. Two groups of investigators, Dmochowski and associates and Gross and co-workers, using the electron microscope, have concluded that more particles sedimentable by means of high-speed centrifugation are present in breast tumors and milks from women with breast cancer than in the milks from apparently healthy women. Bostick has evidence for the presence of a filterable agent capable of causing disease in mice in extracts of lymph nodes from persons suffering from Hodgkin's disease. Schwartz has also reported experimental evidence for a filterable agent in the brains of persons dying of leukemia which will cause leukemia in mice at a time when normally there would be no leukemia. Dmochowski as well as others have obtained electron micrographs of thin sections of lymph nodes of children suffering from leukemia which show particles similar to those found in similar sections from leukemic mice. Whether or not these particles as well as others seen in electron micrographs of thin sections of centrifugally concentrated extracts of different kinds of human cancer tissue actually represent viruses is, of course, not known. Unfortunately, there currently is a tendency to read too much into such findings. It must always be remembered that the cardinal attribute of a virus is its ability to cause replication, and in the absence of proof that a given characteristic particle can bring about replication of itself and cause the disease the particle should not be referred to as virus. The approach involving the

direct examination of human material will, therefore, encounter many difficulties, but in view of the great advances in tissue- or cell-culture techniques I believe not only that the approach should be made but that the activity in this area, especially in leukemia of children, should be intensified. However, there is a strong possibility that human cancer, in part, may require new and different approaches. The relationships involved in animal, bacterial, and plant viruses should be examined carefully for biologically analogous situations which may obtain in human cancer. Certainly, we know that man has coursing through his body many viruses which were unknown a few years ago, and we do not know what many of these are doing there. We know that viruses can persist in their host for generations, in either an infectious or a noninfectious form. We know that viruses can mutate to form new strains that cause different disease symptoms. We know that viruses may have different effects, depending on the age, genetics, and state of nutrition and hormonal balance of the host. We know that different carcinogenic agents can activate subinfectious or latent viruses or prophages, with consequent cellular destruction. It would certainly appear that the activation of prophages by certain chemical or physical agents, with development into a fully infectious bacterial virus and the consequent destruction of the bacterial cells, as well as the phenomenon of transduction by free deoxyribonucleic acid in the pneumococcus and by bacterial viruses in Salmonella, are pertinent to the human cancer problem, especially so in view of the recent discovery of dozens upon dozens of new viruses of man. It is difficult to escape the conclusion that viruses may be the etiological agents for most kinds of cancer, certainly including at least some cancers of man, and that this represents, by far, the most intellectually satisfying working hypothesis which is consistent with all presently known facts. Of the greatest importance is the fact that acceptance of viruses as etiological agents in cancer generally as a working hypothesis will stimulate new experimental approaches to the cancer problem which have been long neglected and which are only now getting started in several laboratories. Could it be that the recent discovery of dozens of hitherto unknown viruses of man which seem to be coursing through our bodies from time to time is but the forerunner of the discovery that specific nucleic acids within our cells, perhaps even of exogenous genetic origin, acquired by transduction or a related phenomenon, have a relationship to our cancers? Certainly, Fraenkel-Conrat's work on infectious nucleic acid should be kept in mind. Needless to say, what we do in the way of experimentation depends in large measure upon what we think, and I am sure the time has come when we should change our thinking with respect to the nature of cancer-virus relationships.

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The Management of Hospital-Acquired Staphylococcal Infections

ELLARD M. YOW, M.D.; MARTHA D. YOW, M.D.; G. KENNETH WOMACK, M.D.; TORU SAKUMA, M.D., and OFELIA T. MONZON, M.D., Houston, Texas

Two conclusions regarding staphylococcal infections appear to be increasingly clear. One is that staphylococci are producing significant numbers of infections among hospitalized patients in all parts of the civilized world, and the other is that the control of this problem requires more than good medical care of the individually infected patient by his personal physician.

The increased concern over staphylococcal disease is evidenced by the number of reports of hospital outbreaks appearing in the medical literature.[1-8] In some hospitals the incidence of infections has reached epidemic proportions, and in others there has been an insidious but definite increase in the number of infections following surgical procedures, complicating viral infections and chronic pulmonary diseases, and associated with the parenteral administration of fluids and drugs. Hospital personnel have contracted infections from patients and in turn spread infection to other patients and members of their families.

The relative importance of the various factors contributing to the increased incidence and severity of staphylococcal infections is not known, but several are playing a significant role (Table 1). One of these factors is the ability of the Staphylococcus to adapt itself readily to survival under unfavorable circumstances. While it is sensitive to the action of many antibiotics, its sensitivity to the commonly used antibiotics is quantitatively considerably less than that of such organisms as the pneumococcus, Streptococcus, and gonococcus, and many strains are naturally resistant to higher concentrations of penicillin, streptomycin, and tetracycline than are attained in the body. The development of resistance of a single strain to an antibiotic during therapy has rarely been a problem, but the selective elimination of sensitive strains and the survival of resistant ones to produce antibiotic-resistant infections have played a significant role in the present problem.

TABLE 1.—*Factors Concerned in the Increased Incidence of Antibiotic-Resistant Staphylococcal Infections*

1. Adaptability of the Staphylococcus
2. Widespread use of antibiotics
3. Increase in complex medical and surgical procedures
4. Longer survival of patients with potentially fatal diseases
5. Feeling of false security with antibiotic coverage; laxity in aseptic techniques
6. Invasiveness and virulence of the Staphylococcus

This selective survival of resistant strains of staphylococci is closely related to the frequency with which antibiotics are used therapeutically and prophylactically.[9] This is illustrated by the rapid rise of antibiotic-resistant strains isolated from hospitalized patients as compared to the strains isolated from patients seen in a physician's office. If one considers only those staphylococci isolated from patients contracting infections after entering the hospital, the situation is even more striking (Fig. 1).

The problem of staphylococcal infections has been further intensified by the complex surgical and medical procedures to which

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From The Departments of Medicine and Pediatrics, Baylor University College of Medicine, and The Ben Taub Infectious Disease Laboratory, Jefferson Davis Hospital.

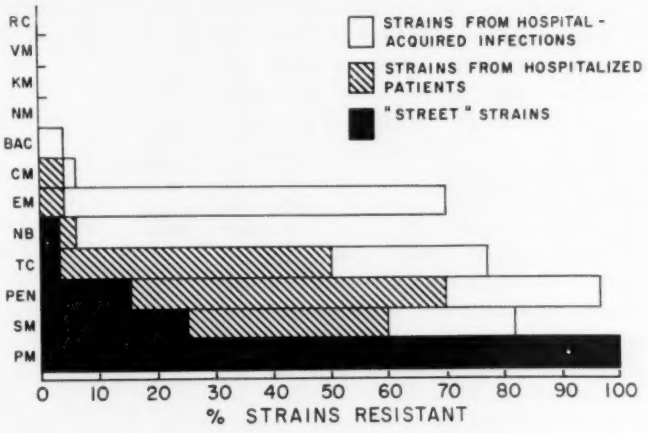

Fig. 1.—The resistance of staphylococci to antibiotics. RC indicates ristocetin; VM, vancomycin; KM, kanamycin; NM, neomycin; BAC, bacitracin; CM, chloramphenicol; EM, erythromycin; NB, novobiocin; TC, tetracycline; PEN, penicillin; SM, streptomycin; PM, polymyxin B.

patients are subjected today. Such procedures as cardiac catheterization, intensive irradiation, and many cardiovascular and pulmonary operations have been made safe partly because of the protective effect of antibiotic therapy. However, if methods for preventing infections cannot be devised or effective therapeutic agents developed more rapidly than the Staphylococcus adapts itself to growth in their presence, many life-prolonging operations may no longer be safe.

Many of the staphylococcal infections have occurred in patients who have potentially fatal diseases but who have been kept living for longer periods by multiple blood transfusions, neoplasm-suppressing agents, vasopressor drugs, artificial respirators, and anti-inflammatory compounds. Many of the patients kept alive by these procedures ultimately reach a point where their defense mechanisms are inadequate to combat the infectious agents to which they are exposed, and the use of "cell-depressing" agents and "infection-spreading" drugs may further contribute to this decreased resistance on the part of the host.

The successful use of antibiotics in preventing and treating infections in the past has lead to a false sense of security on the part of many physicians. Barriers rigidly maintained against the spread of infections in the preantibiotic era have been allowed to sag, and principles of aseptic technique in the operating room, as well as in the entire hospital, have not been consistently applied.

There is no doubt that the widespread and often indiscriminate use of antibiotics has saved many lives. The time has come, however, when the occasional advantages of the prophylactic administration of antibiotics in clean surgical procedures or in the prevention of bacterial infection that might complicate virus diseases must be weighed against the problem of the increasing number of serious infections due to antibiotic-resistant bacteria.

The staphylococci are not the only bacterial species withstanding the effects of the large number of antibiotics used clinically today. Many of the Gram-negative bacilli, particularly the Proteus and Pseudomonas groups, are also frequent causes of antibiotic-resistant infections occurring in hospitalized patients.[10,11] The Staphylococcus has created a greater problem in some instances, however, because of its greater ability to infect the skin and its umbiquity in hospital environments. It also is naturally more virulent in that it has a greater tendency to invade and destroy tissue.

These characteristics of the Staphylococcus have made the management of infections in the hospitalized patient particularly complex. The tendency for minor infections

in one patient to contaminate areas within the hospital and either directly or indirectly to produce serious infections in other patients has made the need for preventive control measures as important as the treatment of the individually infected patient by his personal physician. Aside from the fact that the staphylococcal infections developing in patients admitted to the hospital for other illnesses have created added expense and discomfort, this complication has sometimes failed to respond to the most intense forms of therapy.

During the past winter and spring an epidemic of staphylococcal infections occurred at Jefferson Davis Hospital, providing an opportunity to review the principles of management of staphylococcal infections and experience in evaluating the relative importance of certain control measures. During this epidemic there were 324 recorded infections; 123 of these occurred in the newborn and premature nurseries from Jan. 1, 1958, to May 31, 1958, with 18 deaths. During the same period of time there were 201 hospital-acquired staphylococcal infections among other patients, 150 of which were outpatients and 51, inpatients. Of these 324 patients, the records of 261 have been analyzed as to age incidence, deaths, severity, and site of disease (Fig. 2, Tables 2 and 3). The epidemic has been largely controlled for the present, and the infection rate appears to be lower than the preepidemic level. The reduction in rate of infections was the result of a concentrated and cooperative effort on the part of the hospital administration, the nursing and housekeeping staffs, the house staff, and the members of the various professional services. A hospital Committee on Infections and Antimicrobial Therapy was formed and served as a fact-finding, coordinating, and advisory group to the various services involved (Tables 4 and 5).*

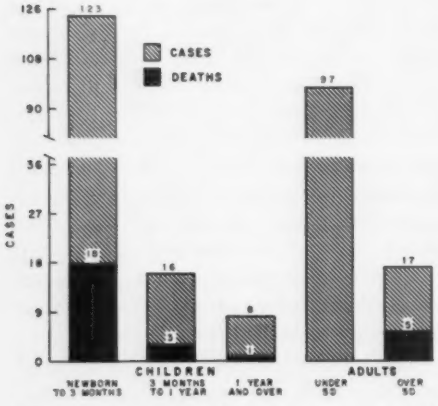

Fig. 2.—Age distribution and deaths in 261 cases of hospital-acquired staphylococcal disease.

TABLE 2.—*Severity of Staphylococcal Infections in 261 Patients*

Category	Number	Deaths
Local		
Mild	85	0
Moderate	96	0
Severe	11	0
Systemic		
Mild	10	0
Moderate	22	0
Severe	47	34(72%)
Total	261	13%

*Members of the Standing Committee on Infections and Antimicrobial Therapy: Dr. Phil Davis, Dr. James D. McMurrey, Dr. Martha Yow, Dr. Harold Daily, Dr. Benjamin Sher, Dr. George Ellis, Dr. John Gannon, Dr. John Vaughn, Dr. James Crawley, Dr. John Knox, Dr. Russell Scott Jr., Dr. Robert R. Jackson, Dr. Moses Ashkenazy, Dr. Ben T. Withers, Dr. Don Ford, Dr. Jane Telford, Miss Elinor Hamner, Mrs. Dorothy Harper, Mr. A. S. Reaves, Dr. S. B. Hardy, Dr. William Bell, Dr. Richard Eppright, Dr. Harry Davis, and Dr. Ellard M. Yow.

TABLE 3.—*Sites of Infection in 261 Cases of Hospital-Acquired Staphylococcal Disease*

Sites	Number	%
Maternal breast abscesses	63	24
Pyoderma	44	17
Subcutaneous abscesses	38	15
Septicemia	36	14
Surgical infections	20	8
Pneumonia	18	7
Infant breast abscesses	17	6
Gastroenteritis	9	3
Conjunctivitis	5	2
Meningitis	3	1
Others	8	3

TABLE 4.—*Standing Committee on Infections and Antimicrobial Therapy*

Objectives
1. To coordinate the study and control of infections among hospital patients and personnel
2. To encourage the judicious use of antimicrobial agents
Organization
1. Composed of a chairman representative of each professional service, the nursing department, and the hospital administration
2. Serves in an advisory capacity to the medical board of the hospital and the hospital administration
3. Standing subcommittees

The following discussion is based largely on the approach to the control of the infection utilized at Jefferson Davis Hospital.

Committee on Infections and Antimicrobial Therapy

It is now generally recommended that one of the most important measures for control of hospital infections is the establishment of committees on infections.[12] Since the use of antibiotics is directly related to the increase in antibiotic-resistant strains of bacteria and the careful selection of appropriate antibiotics is important in the treatment of infection due to these organisms, it is desirable to have the Infections Committee also charged with the responsibility of making

TABLE 5.—*Subcommittees of Standing Committee on Infections and Antimicrobial Therapy*

Name	Members	Responsibilities
1. Service Subcommittees (one for each professional service, including nursing service).	Chairman: representative on Committee on Infections. Members: Key members of department and appropriate house officers.	1. To act in liaison capacity between parent committee and service it represents. 2. To be responsible for survey and control of infections on service and the use of antimicrobial agents (as delegated by chief of service).
2. Reporting and Recording Infections.	Nursing service, a professional service, and hospital administrator.	1. To keep daily records of patients with infections in hospital and clinic. 2. To report these to appropriate services.
3. Housekeeping Practices Influencing Spread of Infections.	Representatives of Housekeeping Department, Nursing Service, Professional Service, and a hospital administrator.	1. To review housekeeping practices and make recommendations for alterations pertinent to particular hospital problem. 2. To enlist aid of public health facilities available to review these practices.
4. Isolation of Infected Patients.	Pediatric, obstetrical, nursing, medical, and surgical representatives.	1. To make recommendations for handling infected patients in hospital and clinic. 2. To make recommendations regarding general isolation techniques in hospital.
5. Survey and Management of Staphylococcal Carriers.	Epidemiologist, and representatives of Pediatric and Obstetrical Services.	1. To decide to what extent surveys of carriers are to be carried out and to arrange for surveys. 2. To report to service subcommittees results of surveys with recommendations for control.
6. Laboratory Facilities and Procedures.	Representatives of Laboratory Service and appropriate personnel of Research and Public Health Laboratories.	1. To review facilities for appropriate laboratory procedures. 2. To standardize procedures utilized in different laboratories and to delegate performances of special procedures.
7. Chemotherapy and Chemoprophylaxis.	Infectious disease section representatives.	1. To make general recommendations regarding use of antimicrobial agents therapeutically and prophylactically. 2. To evaluate the injudicious use of these agents.
8. Management of Hospital-Acquired Infections.	Representatives of Infectious Disease Sections.	1. To make recommendations regarding the routine treatment of patients acquiring infections within hospital. 2. To establish special clinics for handling nonhospitalized infected patients.
9. Public Relations and Personnel Education.	Hospital Administrator; Chief of Medical Staff; Chairman, Committee on Infections, and Nursing Service Representative	1. To control the release of information concerning infection to public. 2. To organize educational programs for hospital personnel.

recommendations regarding the judicious use of antibiotics.

The precise organization of this committee should be adjusted to the needs of an individual hospital but should include representatives of all major professional services, the nursing and housekeeping services, the laboratory service, and the hospital administration. Where practical, persons in an immediate supervisory capacity should serve as the representatives for each service, since the participation in the formation of plans is in itself highly informative and the cooperation in carrying out the recommendations of the committee will be closely related to the understanding of the thinking behind the decisions of the committee.

The committee should act as a fact-finding group and should make recommendations concerning the control of infections to the hospital administration, to the governing professional board of the hospital, and to specific services when indicated. Rules and regulations should not be made by this committee but by the appropriate administrative divisions of the hospital, using as a basis the recommendations of the committee.

Where the incidence of infection is great or an actual epidemic occurs, much can be gained by having a series of service subcommittees for each hospital service. The representative of each service appointed to the Committee on Infections and Antimicrobial Therapy should serve as the chairman of the service subcommittee for his particular service. He should appoint members of his service who have the direct responsibility of patient care to serve with him on this subcommittee. These persons will often be house staff personnel.

This service subcommittee acts as a liaison between the individual service and its professional chief and the Infections Committee. It serves to report to the Infections Committee problems related to infections and the use of antimicrobial agents occurring on the service and in turn conveys the thinking behind the recommendations of the Infections Committee to the members of the service.

The service subcommittee should also see that the policies adopted by the hospital administration regarding the control of infections and the use of antibiotics are properly followed and should check on the accuracy of the reporting of infections from its service. The Infections Committee and the administration should call on the service subcommittee for help when breaks in control measures occur and for aid in the survey and management of carriers.

Reporting Hospital Infections

A subcommittee of the Committee on Infections and Antimicrobial Therapy should be established to set up methods of reporting and recording infections. This committee should include a member from the surgical service, the laboratory service, the nursing service, and the services whose infection rate is unusually high. Some decision must be made as to what actually constitutes a reportable infection. It is obvious that not all "positive cultures" represent significant infections. An effort should be made to determine which infections are acquired after the patient was admitted to the hospital and what factors contributed to the development of the infection.

At Jefferson Davis Hospital it was felt that the actual reporting could be best made by the nursing supervisor on each floor at a regular time each day. She would obviously need the help of physicians having patients on the floor in deciding which infections should be reported. The Committee on Records and the service representative should periodically cross check on the accuracy and completeness of these reports. Patients coming to the emergency room and various clinics should also be reported, particularly if they have previously been admitted to the hospital or treated as outpatients.

The Committee on Infections and Antimicrobial Therapy should meet at least monthly to review the infection rate and the effectiveness of various control measures.

Where infections rates are high, a committee office should be established where

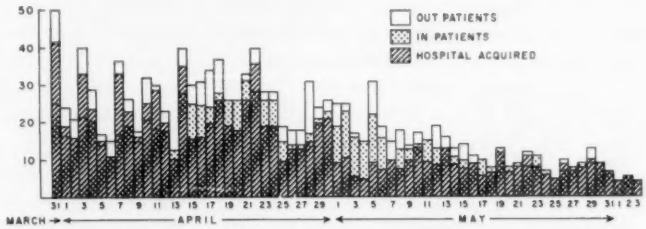

Fig. 3.—Daily census of Staphylococcus infections among patients at Jefferson Davis Hospital.

records are maintained on patients with hospital-acquired infection. Appropriate graphic charts are helpful in indicating trends in infection rates (Fig. 3). Additional records should be kept by individual services where special problems exist.

Evaluation of Housekeeping and Nursing Procedures Influencing Spread of Infections

As has been emphasized by all authors discussing the hospital staphylococcal problem, the single most important factor in the control of this nosocomial infection is good environmental hygiene. Methods of achieving this have been succinctly outlined by the Temple Hospital group,[4] by Brown,[13] and by many others. Utilizing the experience of these investigators, recommendations of the State Sanitary Engineer, and findings of surveys by the Subcommittee on Housekeeping and Nursing Procedures of the Infections Committee, certain changes in physical facilities, housekeeping procedures, and nursing techniques were instituted at Jefferson Davis Hospital. Serial air studies for bacterial counts in various locations and bacterial studies of fomites were of considerable aid in locating "danger spots." Some of the more important corrective measures designed to lower the rate of hospital-acquired infections are summarized in Tables 6, 7, and 8.

During the height of the outbreak at Jefferson Davis Hospital there was a daily

TABLE 6.—*Measures Designed to Improve Physical Facilities Contributing to Spread of Infection*

I. Proper management of air flow throughout hospital units and frequent changing of air-conditioner filters
II. Lessening of crowding by provision of emergency obstetric and nursery units
III. Provision of proper dressing rooms for personnel
IV. Provision of additional bathing facilities for patients
V. Provision of adequate handwashing facilities for personnel and patients
VI. Provision of isolation area for all proven staphylococcal cases in one area of the hospital and "suspect" rooms on each individual service

TABLE 7.—*Improvements Emphasized By Nursing Staff*

I. Use of methods of detection of personnel "off limits" or in improper dress
  1. Identification plates for each employee showing area to which assigned.
  2. Different colored scrub clothes for nurseries, obstetrical service, and operating room.
II. Rigid control of visiting, both by outsiders and between hospital patients.
III. Reeducation of professional and nonprofessional personnel in the practice of proper isolation techniques.
IV. Assignment of personnel in such a manner as to reduce cross traffic between "clean" and "dirty" areas.
V. Policing of operating room, maternity suite, and nurseries to prevent entry of unnecessary persons.
VI. Use of individual autoclaved dressing sets and proper care of soiled instruments and dressings.

TABLE 8.—*Improvements in Housekeeping Policies*

I. Institution of rigid dust control program.
  A. Wet-mopping stairs with germicidal solution.
  B. Coating floors with plastic finish to eliminate use of rotary buffing machine.
  C. Mopping floors with chemically treated mops, autoclaved at regular intervals. Elimination of dry sweeping and vacuum cleaning.
  D. Use of teaching films on dust control.
II. Proper handling of waste material.
  A. Frequent sterilization of waste receptacles and use of disposable liners.
  B. Careful covering of garbage removal carts with chemically treated daily autoclaved cloth covers.
III. Intensified antiseptic scrubdowns in nurseries and operating and recovery rooms.
IV. Removal of unnecessary equipment from corridors and rooms.
V. Proper handling of clean and soiled linen.
VI. Provision of mattresses with plastic covers.
VII. Proper sterilization of bed pans and use of disposable covers.
VIII. Rigid pest control.

meeting of the representatives of the housekeeping staff, nursing staff, administrative staff, nursery service, obstetrical service, and the epidemiologic nurse assigned by the Communicable Disease Division of the U. S. Public Health Service. The purpose of this *ad hoc* committee was to report on the practicality and effectiveness of the corrective measures. This discussion between the various services was indispensable to the implementation of the plan of control.

Another factor contributing to the success of the control of infections was the sponsorship by the nursing department of a hospital improvement contest. The purpose of the contest was to inspire individual pride in the maintenance of high standards of work in personnel, professional and nonprofessional.

Isolation of Infected Patients

There is little precise information concerning the relative importance of various methods of spread of staphylococcal infection within the hospital. Experience at Jefferson Davis Hospital was consistent with the opinion of others in that the evidence suggested that the infected patient or employee served as the most important source of spread.[4,14] Consequently every effort should be made to recognize infections as soon as possible in order to prevent exposure of other persons. It is important not only to remind the physicians and nurses constantly of this fact, but the housekeeping and dietary departments, technicians, and all of the various groups working in the hospital should be clearly informed of the importance of relatively minor infections of the skin in disseminating staphylococci. Persons working in the hospital should be urged to report suspicious lesions to their supervisors before going on duty, and a physician should be available to inspect these lesions and to remove the person from duty until the danger of spread has been removed. Complete cooperation in this matter cannot be assured unless the hospital continues to pay its personnel when they are required to lose time from their jobs because of infections.

Whenever possible patients with antibiotic-resistant staphylococcal infections should be managed as outpatients in order to reduce further contamination of the hospital and spread of infection. At Jefferson Davis Hospital it was found desirable to set up a special outpatient clinic in an area physically separated from other clinics and with personnel not working in other areas in which highly susceptible patients were seen. This clinic was organized for the purpose of inspecting and treating potentially infected or infected patients and nasal carriers.

Infected hospitalized patients should be physically separated in isolation units with separate attending personnel. It may be necessary under some circumstances to isolate less severely infected patients on general floors. The degree and duration of the isolation should depend on the amount of infected material exuding from the patient.

Newborn infants are particularly susceptible to staphylococcal infection and may actually serve as a reservoir of infection within a hospital.[8] Consequently, it is especially important to control infection in this group of patients. Nurseries physically separated and with separate personnel should be established to include areas for (1) uninfected infants of normal deliveries, (2) uninfected infants born of complicated deliveries, (3) infants suspected of having infections and infants born outside of the hospital, and (4) infants having definite infections.

Detection and Management of Nasal Carriers

Early in the course of the Jefferson Davis Hospital outbreak it became evident that the phage type of Staphylococcus causing the major portion of the hospital-acquired infections was 42B,81, 44A,70.† A program for detection of the persons carrying this

†Phage typing was performed by Dr. J. V. Irons, Director of Laboratories, State of Texas Department of Health, Austin, Texas.

strain was instituted. In addition, attention was directed to all persons harboring "triply resistant" strains. The latter was employed as a rapid-screening method since phage typing was performed at the state laboratory in another city, necessitating some delay.

Much information is available regarding nasal carrier rates among hospital workers. Surveys during hospital epidemics have revealed rates ranging from 4% to 17.7%.[4,6,15] All investigators have found that the rate is significantly higher in professional staff than in lay employees.[16] Preliminary studies during the height of the Jefferson Davis Hospital epidemic revealed that 7.8% of the first 370 employees studied harbored phage Type 42B,81, 44A,70, on at least one occasion. The experience at this hospital matched those of others[15] in that the majority of persons from whom this strain was isolated were nurses, doctors, and attendants involved in patient care in areas of the hospital where the greatest numbers of staphylococcal patients were being cared for. The experience of Rountree[16] in 1956 suggested that the carrier gave the infection to the patient. However, other more recent articles, including one by Bass and associates,[15] indicate that the patient is a hazard to the attending personnel.[13]

The role of the staphylococcal nasal carrier remains unsolved. This is a problem which deserves further investigation, since continuous cultural surveys are a time-consuming, unwieldy, and expensive operation. If they are of limited or no value they should be abandoned.

Management of the nasal carrier is also unsettled. It has varied from administration of systemic antibiotic therapy[15] and removal from duty to mere apprisal of the person of his positive culture.[4] The use of systemic antibiotics for nasal carriers has been abandoned generally, since it creates more problems than it solves. Most hospitals are suggesting either the use of local antibiotic ointments or no therapy.[4,15,16] At present, attempts are being made at Jefferson Davis Hospital to evaluate the use of a local bacitracin spray.

Review of Indications for Use of Antibiotics Therapeutically and Prophylactically

The high incidence of antibiotic-resistant strains of bacteria in hospitals is largely due to increasing amounts of antibiotics used therapeutically and prophylactically.[8,17] Consequently, each hospital and each service should, by reviewing objectively its own experience and the experience of trained investigators, decide on principles of administration of antimicrobial agents applicable to its particular circumstances. The process of reevaluating the evidence for the use of antibiotics for an individual disease will in itself be informative and lead to more thoughtful and judicious use of antibiotics. Members of the visiting staff and house staff should critically review particularly the evidence for the prophylactic administration of antibiotics. The increased concern over the indiscriminate use of antibiotics at Jefferson Davis Hospital led to a gradual decrease in the antibiotic costs from $13,103.61 to $5819.51 per month over a five-month period. This occurred during the time that the hospital infections were high (Figs. 4 and 5).

The Subcommittee on Chemotherapy and Chemoprophylaxis should report to the Infections Committee its recommendations concerning the use of antibiotics, and if the general principles recommended are agreed upon by the various service representatives, they should be distributed among the house

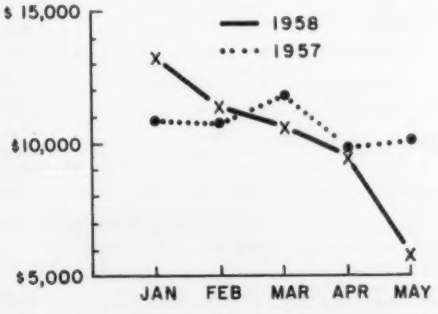

Fig. 4.—Cost of antibiotics dispensed monthly from pharmacy.

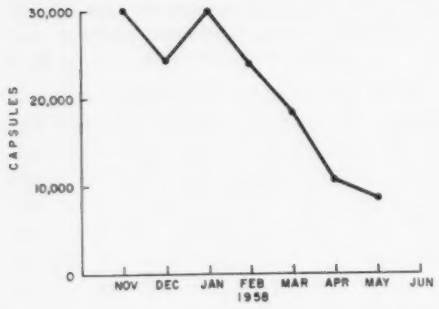

Fig. 5.—Tetracycline dispensed at Jefferson Davis Hospital.

and visiting staff as general guides to therapy.

Therapy of Hospital-Acquired Staphylococcal Infections

The major difference in the treatment of the patient with a hospital-acquired staphylococcal infection from that of the patient acquiring his infection outside the hospital (Tables 9 and 10) is in the selection of the antistaphylococcal antibiotic to be used. This is a direct reflection of the frequency with which nosocomial strains are resistant to the commonly used antibiotics. At Jefferson Davis Hospital, for example, 97% of these strains were resistant to penicillin, 82% were resistant to streptomycin, 78% were resistant to tetracycline, and 70% were resistant to erythromycin. The chance that an individual strain of Staphylococcus will be sensitive to a particular antibiotic will vary depending on the extent of the usage of antibiotics in the individual hospital, but most strains isolated from hospital-acquired infections are resistant to penicillin, streptomycin, and tetracycline.[17] Consequently,

TABLE 9.—*Therapy of Hospital-Acquired Staphylococcal Infections*

1. Neither penicillin, streptomycin, or tetracycline should be used unless there is laboratory evidence indicating specific strain sensitivity.
2. Local physical, antibiotic, and surgical therapy when indicated.
3. Systemic antibiotic therapy.
   (a) Mild to moderately severe infection: Bacteriostatic drugs.
   (b) Moderately severe to severe infection: Bactericidal or bactericidal plus bacteriostatic agent.

TABLE 10.—*Antistaphylococcal Antibiotics*

Drug	Route	Daily Dosage: Adults, Gm.	Daily Dosage: Children, Mg/kg.	Side Effects	% Hosp. Strains Sensitive *
I. Bacteriostatic					
1. Tetracycline	Oral	1-2	30-50	Hypersensitivity	22
	I. M.	1-2	30-50	Gastrointestinal irritation	
	I. V.	1-2	30-50		
2. Chloramphenicol	Oral	2-3	30-100	Rare bone marrow injury Gastrointestinal irritation	95
	I. M.	1-2	30-80		
	I. V.	1-2	30-80		
3. Erythromycin	Oral	1-2	20-50	Gastrointestinal irritation	30
	I. V.	1-2	20-50		
4. Novobiocin	Oral	1-2	20-50	Hypersensitivity reactions	95
	I. V.	1-1.5	20-30		
5. Oleandomycin	Oral	1-2	20-50	Gastrointestinal disturbance	95
6. Ristocetin	I. V.	2-8	50-200	Skin rash Thrombophlebitis	100
II. Bactericidal					
1. Penicillin	I. M.	1,000,000-10,000,000 Units	50,000-150,000 Units	Hypersensitivity reactions	3
2. Streptomycin	I. M.	1-3	30-50	Damage to 8th cranial nerve Hypersensitivity reactions	20
3. Bacitracin	I. M.	40,000-100,000 Units	600-1,200 Units	Nephrotoxicity and pain on injection	98
4. Neomycin	I. M.	1	15	Nephrotoxicity and ototoxicity	100
5. Vancomycin	I. M.	2-4	50-100	Local thrombophlebitis, Skin rash Rarely ototoxic	100
6. Kanamycin	I. M.	1-3	10-50	Ototoxic and ? nephrotoxic	100

* Jefferson Davis Hospital.

these antibiotics should not be used routinely and should be used in an individual patient only if there is laboratory evidence indicating sensitivity of the specific strain. At Jefferson Davis Hospital novobiocin, chloramphenicol, and oleandomycin ‡ have been used for limited indications and most strains have remained sensitive to these antibiotics.

In severe staphylococcal infections it is desirable not only to select the agent to which the causative organism is sensitive in vitro but to select one which has the greatest killing power.[17] It is important to differentiate between those antistaphylococcal antibiotics which are predominantly bacteriostatic in their action and those which are bactericidal. The severest form of staphylococcal septicemia is acute staphylococcal endocarditis. Successful therapy of such forms of staphylococcal disease usually requires the administration of antibiotics which are highly bactericidal, such as vancomycin,§ kanamycin,‖ neomycin, and bacitracin, and, when individual strains are sensitive, large doses of penicillin and streptomycin. Less severe septicemias may respond to such bacteriostatic agents as novobiocin, ristocetin,¶ chloramphenicol, erythromycin, oleandomycin, and tetracycline.

In addition to the differences in their effect on various strains of staphylococci, the antistaphylococcal drugs have other differences in route of administration and tolerance. The intramuscular route is the preferable method of administering kanamycin, neomycin, and bacitracin; ristocetin and vancomycin must be given intravenously. While none of these drugs can be given orally, this is no particular disadvantage in seriously ill patients, since they can usually be best treated by the parenteral route. Erythromycin, novobiocin, and tetracycline can be administered orally and intravenously, but intramuscular preparations of these drugs are not entirely satisfactory. Chloramphenicol can be given orally, intravenously, and intramuscularly, although the initial rise in blood level following intramuscular injection is not high.

Hypersensitivity reactions occur with some frequency in association with novobiocin therapy, especially if the dosage is great, and less frequently with ristocetin and vancomycin. The ototoxicity and nephrotoxicity of neomycin is observed with sufficient frequency to limit its use to patients failing to respond to other agents. Ototoxicity is apparently also rarely associated with therapy with vancomycin and kanamycin.

Although extremely active antistaphylococcal agents are available today, none of these agents will adequately penetrate the barriers of walled-off infections, avascular hematomas, or nonviable tissue. If an infection is treated prior to abscess formation or if the abscess is quite small, surgery can sometimes be avoided, but under most circumstances it is still important to drain staphylococcal abscesses. Local compresses or soaks may aid in spontaneous drainage or supplement surgical drainage.

A point of some importance in the management of staphylococcal infection is the evaluation of the role of local antibiotic administration. In certain types of localized infections, such as empyema, purulent pericarditis, and septic arthritis, the local instillation of neomycin or bacitracin is highly effective in suppressing the staphylococci. More recently kanamycin is being evaluated because of its relative freedom from toxicity.[18,19] Where a nonirritating solution is desirable the concentration of neomycin or kanamycin should be 2.5 mg. per milliliter and bacitracin 200 units per milliliter. In grossly infected areas more concentrated solutions may be used, but the total daily dose of neomycin should not exceed 1.0 gm.; kanamycin, 3.0 gm., and bacitracin, 100,000 units.

‡Oleandomycin was supplied by Pfizer Laboratories, Division of Chas. Pfizer & Company, Inc., as Tao and by Wyeth Laboratories, Inc., as Cyclamycin.

§Vancomycin was supplied by Eli Lilly & Company as Vancocin.

‖Kanamycin was supplied by Bristol Laboratories, Inc., as Kantrex.

¶Ristocetin was supplied by Abbott Laboratories as Spontin.

Another approach to local prophylaxis of staphylococcal infections in wounds is being tried in Houston. A combination of bacitracin and neomycin or kanamycin is being instilled at the time of surgery in traumatic wounds or surgical procedures that are likely to be associated with the formation of hematomas or collections of transudate. This presumably has the advantage of the antibiotics being incorporated in the hematoma as it is formed rather than having to depend on the diffusion into the area by the systemic administration of an antibiotic. This approach may be particularly important in cardiovascular, neurosurgical, or other operations where infection is likely to be very serious if it occurs.

Summary

The management of hospital-acquired staphylococcal infections differs from those developing in patients outside a medically influenced environment in that they are likely to be due to strains of bacteria resistant to the commonly used antibiotics and in that intensive control measures must be undertaken by the entire hospital staff to prevent relatively minor infections in some patients from producing serious infections in others.

The principle control measures should be coordinated by a hospital Committee on Infections and Antimicrobial Therapy composed of representatives of all the hospital professional services, the housekeeping department, and the hospital administration. This committee should serve as a fact-finding and advisory group, studying the incidence of infection, the factors contributing to the spread of infection, and the effectiveness of control methods, and should organize an educational program to stimulate the judicious use of antimicrobial agents.

Where abscesses exist surgical drainage is required, but therapy with appropriate antibiotics tends to localize the infection and aids in controlling the bacteremia.

Penicillin, streptomycin, and tetracycline are rarely active against the hospital strains of staphylococci. Mild to moderately severe infections should be treated with novobiocin, chloramphenicol, ristocetin, erythromycin, or oleandomycin. Severe infections require such actively bactericidal agents as kanamycin, vancomycin, or bacitracin.

Baylor University College of Medicine, Departments of Medicine and Pediatrics.

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Experience with Amphotericin B for the Treatment of Systemic Mycoses

JOHN H. SEABURY, M.D., and HARRY E. DASCOMB, M.D., New Orleans

Amphotericin B is an antibiotic produced by a species of Streptomyces. It appears to have no important antibacterial properties, but possesses highly significant activity against those yeast-like fungi which produce deep mycotic infection in man. Table 1 contains the in vitro sensitivities of the major producers of deep mycotic infection in man as determined by various investigators.[1-3] Our own findings, on Sabouraud's dextrose agar at pH 7, are indicated in the Table.

Studies in experimental animals [2,3] have indicated a good correlation between in vivo effectiveness and in vitro sensitivity to amphotericin B. Animal toxicity studies carried out by the Squibb Institute for Medical Research indicated that amphotericin B had a therapeutic index sufficient to justify clinical trial in human mycotic infections. Several reports [4-6] of its use in histoplasmosis and cryptococcosis have already appeared in the American literature.

Routes of Administration and Toxicity

The insolubility of crystalline or amorphous amphotericin B in water may be modified slightly by changing the pH of the solvent to 2 or 11. Even under these conditions, the solubility does not exceed 0.2 mg. per milliliter. Early trials [3] indicated that absorption of orally administered amphotericin B did occur but that this was quite irregular from patient to patient. Relatively large doses were required to achieve significant blood levels. Crystalline amphotericin B, amorphous amphotericin B, and mixtures of amphotericins A and B have all been distributed by Squibb for clinical and laboratory study. Some of our patients received oral amphotericin B of the crystalline type, and some received a mixture of amphotericins A and B.

In 1956 a suspension of amphotericin B in saline became available for parenteral use. The first patients treated intravenously by us received this material. The suspension had several obvious defects. Very frequent agitation of the suspension in the infusate of 5% dextrose was necessary to prevent sedimentation and loss of the drug. Furthermore, drug dispersion was not uniform, and rather large amounts might be infused within a relatively short time, resulting in severe reactions. If an infusion set with a filter was used, a variable but very significant amount of the antibiotic was found trapped within the filter. The exact dose received by the patient with this material was always conjectural.

In December, 1956, a new preparation of amphotericin B * became available for parenteral use. The antibiotic was combined with approximately 33 mg. of sodium deoxycholate per 50 mg. of amphotericin B, and this was buffered with sodium phosphate and lyophilized. When reconstituted in water for injection, U. S. P., or in 5%

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From the Department of Medicine of Louisiana State University Medical School and the Lung Station of Charity Hospital.

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*Amphotericin B is produced by E. R. Squibb & Sons under the trade name of Fungizone.

TABLE 1.—*Minimal Inhibitory Concentration of Amphotericin B for Certain Pathogenic Fungi*

Organism	Determined by Others, μg/Ml.	Determined by Us, μg/Ml.
Blastomyces dermatitidis	0.5	0.06 (3 strains)
Candida albicans	0.5-3.7	2.0
Cladosporium trichoides		1.0
Coccidioides immitis	0.5	0.4
Cryptococcus neoformans	0.03-0.6	0.06-0.6
Histoplasma capsulatum	0.04-0.9	0.4-0.6
Sporotrichum schenckii		
Yeast phase	0.07-0.14	0.1-0.5
Mycelial phase	>40	>3.0

dextrose injection, U. S. P., it formed a clear golden fluid which had the gross characteristics of a solution even though it was actually a colloidal suspension. This material is much more satisfactory for clinical use. For convenience in tabulation, we have used the symbol I to represent the first type of suspension of amphotericin in saline and the symbol S to represent the sodium deoxycholate preparation.

During the treatment of patients with amphotericin B we have had the opportunity to administer this substance orally, intravenously, intramuscularly, intrathecally, by local instillation, and by aerosol. Table 2 lists our evaluation of the antibiotic when administered by these routes. Bioassay and clinical results indicated that the intravenous route was the most effective.

We found that amphotericin B, when dissolved in 1% procaine with the addition of 20-25 mg. of sodium succinate ester of hydrocortisone, could be administered intramuscularly without any more local reaction than commonly follows injections of 1 gm. of streptomycin. Unfortunately, we were unable to detect any amphotericin activity in the blood serum of patients receiving single or multiple intramuscular injections of the solubilized antibiotic (up to 1 mg. per kilogram of body weight). Blood samples were drawn at 2, 4, 8, and 24 hours after injection in one patient and at 1, 2, and 4 hours after injection in two patients. The addition of hyaluronidase to the injection did not alter the findings in one patient. Clinical observation of one patient with cutaneous lesions of blastomycosis which failed to improve during intramuscular treatment strengthened the significance of the assay evidence.

Intrathecal administration was likewise well tolerated in the dosage and manner used by us. The material was dissolved in water for injection, U. S. P. After the withdrawal of spinal fluid for laboratory studies, 20 mg. of the sodium succinate ester of hydrocortisone was instilled through the spinal needle. The syringe was then removed, and 1 mg. of amphotericin was diluted with spinal fluid to 3 ml. in a second syringe and *slowly* reinjected. The colloidal suspension (S form) is somewhat heavier than spinal fluid, and paresthesias frequent-

TABLE 2.—*Routes of Administration of Amphotericin B* *

Route	Local Tolerance	Systemic Side-Effects	Range of Dosage, Mg/Kg.	Response
Oral	Good	None	242-50	Slight
I. M.	Acceptable †	Mild or none	1.0-0.28	None
I. V.	Good	Mild or moderate	3.0(I)-0.46(I) 1.3(S)-0.25(S)	Good aginst susceptible organisms
I. T.	Acceptable †	Mild	Not related to body weight; 1 mg. only	Probably useful
Local instillation	Good	None	Not related to body weight; up to 30 mg. in a pyoarthrosis	Good against susceptible organisms
Aerosol	Acceptable	None	Not related to body weight; up to 25 mg/day	Not known

* The following abbreviations are used in Tables 2 to 7 inclusive: I. M., intramuscular; I. V., intravenous; I. T., 1 mg. amphotericin B intrathecally; (I), suspension of insoluble amphotericin B; (S) "solubilized" amphotericin B; q. o. d. every other day.
† Acceptable when combined with adjunctives; see text.

ly appeared in the segments innervated by dependent roots. We do not advise intrathecal injection more often than twice each week.

Spinal fluid assays during the course of intravenous treatment suggested a direct relationship between the level of spinal fluid protein and the concentration of amphotericin appearing in the fluid. The amount of spinal fluid protein seemed more important than the intravenous dosage of amphotericin. Our observations are recorded in Table 8. The highest concentration of amphotericin found in the spinal fluid was 0.46μg. per milliliter. Two patients with normal spinal fluid proteins had no assayable level (0.04μg. per milliliter) of amphotericin in the spinal fluid despite adequate intravenous dosage (0.73 mg. and 0.83 mg. per kilogram). One of these two patients was receiving intrathecal amphotericin (1 mg.) every third day during the time of study. In this patient 13 different spinal fluid samples drawn 72 hours after intrathecal and 24 hours after intravenous amphotericin were devoid of detectable antibiotic. However, after treatment had been interrupted for one month, the spinal fluid protein rose to 78 mg. % and amphotericin could be detected in the spinal fluid after intravenous therapy only.

One patient (Patient 13) was given 1 mg. of amphotericin intrathecally while receiving no other amphotericin. The spinal fluid level 24 hours later was 0.33μg. per milliliter. Two daily intrathecal injections of 1 mg. each gave the same level of amphotericin 48 hours after the last injection and produced toxic manifestations. A second patient (Patient 16) had essentially the same spinal fluid level of amphotericin 24 hours after 1 mg. of intrathecal amphotericin. At 48 hours the level was 0.17μg. per milliliter, and none was present 72 hours after the injection despite the fact that he was receiving intravenous amphotericin concurrently.

No significant reactions were observed following the local instillation of amphotericin into abscesses, areas of osteomyelitis, and suppurative lymph nodes. Used in this manner, it was fungicidal in large doses. Up to 30 mg. of the solubilized antibiotic has been injected into suppurated lymph nodes and pyoarthroses. Doses of 50 mg. and 75 mg. of the insoluble suspension have been given intrapleurally.

Intravenous administration appears to be the route of choice at present. Table 3 lists the side-effects and toxicity experienced by us during the intravenous treatment of 18 patients. After many trials of various infusion times, we found that reactions with solubilized amphotericin were no severer when the calculated dose was administered in 500 ml. of 5% dextrose injection, U. S. P., over a period of two or three hours than when the same dose was given over a much longer time or in greater dilution. With one exception, all patients experienced rigor and moderate fever during the first few infusions of amphotericin. With continued daily administration the degree of reaction decreased. Rigor disappeared first. Reactive fever then subsided. However, we observed that when a new lot number of antibiotic was given, reactions reappeared temporarily. In our experience, the addition

TABLE 3.—*Toxicity of Intravenous Amphotericin B*

Type of Reaction	Proportion of Patients Having Reaction *	Comment
Chills & fever	17/18	1 patient had single chill
Headache	7/18	
Nausea	4/18	At high dosage
Vomiting	1/18	
Anorexia	10/18	At high dosage
Abdominal pain	8/18	At high dosage
Nitrogen retention	6/18	Treatment interrupted in only 1 patient
Melena	1/18	No ulcer demonstrated
Phlebitis	1/18	
Hemorrhagic gastroenteritis	1/18	At necropsy
Blurring of vision	1/18	Repeatedly during infusion
Exfoliative dermatitis Purpura Convulsions Death	1/18	All in 1 infant at high dosage

* Patients 10 and 18 with cryptococcal meningitis are not included because of their unconscious state.

of an antihistaminic reduced the degree of reaction to infusion. Whenever reactions persisted or became excessive, the addition of 25 mg. of sodium succinate ester of hydrocortisone was very effective in reducing the reaction.

Currently we initiate intravenous therapy with a dose of 0.25 mg. per kilogram of body weight. This amount is increased by 5 mg. each day or every other day, according to the degree of reaction and urgency of the situation. The maximum tolerated dose may be somewhere between 0.5 mg. and 1.5 mg. per kilogram.

Only one patient presented therapeutic difficulties because of phlebitis. This patient was treated in a hospital where intravenous fluids were administered by nurses. One patient received amphotericin intravenously daily for many months without presenting any problems in administration.

Headache and nausea accompanied the initial infusions of amphotericin in some patients but usually were not severe. At high dosage, these symptoms occasionally reappeared and necessitated lowering of the dose. Anorexia appeared independently of nausea. This symptom was much more frequent than nausea and became a problem at high doses. Fortunately, it decreased food intake seriously only at the meal which accompanied or followed the infusion.

According to the Squibb Institute for Medical Research, intravenous amphotericin can produce diffuse hemorrhage throughout the small intestine and colon of dogs. We have observed this in man. One patient (Patient 5) with blastomycosis complained bitterly of epigastric and abdominal cramping pain during and for several hours following infusions of solubilized amphotericin at doses above 0.5 mg. per kilogram of body weight. Symptoms were not relieved by antacids and only slightly by anticholinergics. He died of acute staphylococcal pneumonia several days prior to the planned termination of treatment. Necropsy showed moderately severe congestion and petechial hemorrhage involving the mucosa of the gastric antrum, small bowel, and rectum. The colon was not involved. Another elderly patient with blastomycosis had the same complaints together with severe anorexia during the latter part of his intravenous treatment. He developed melena which required three 500 ml. blood transfusions and interruption of antibiotic therapy. Gastrointestinal x-rays revealed hyperirritability and pylorospasm but no ulcer. We suspect that melena in this patient was due to a similar mechanism as that observed at necropsy in the first patient. All of the eight patients who complained of abdominal pain characterized it as cramping in nature and severest in the epigastric region.

None of our patients developed nitrogen retention while receiving the insoluble suspension of amphotericin. Treatment with the solubilized antibiotic was accompanied by an elevation of the blood urea nitrogen above 20 mg. % in six patients. Azotemia was not accompanied by other evidence of renal damage. When nitrogen retention developed, we usually decreased the daily intravenous dose by 25%-30%. Under these conditions azotemia was transient. In two patients we elected to continue intravenous amphotericin at 10%-20% lower dosage. The blood urea nitrogen returned to normal gradually over many days in one but remained elevated in the second until dosage was further reduced. A 15-year-old boy (Patient 16) with no previous history of renal disease did not follow the above course. His blood urea nitrogen became elevated at an amphotericin dosage of approximately 0.7 mg. per kilogram of body weight. When the blood urea nitrogen was 26 mg. %, the dosage of amphotericin was decreased 12%. Nitrogen retention increased, and the dosage was reduced by 30%. Despite this 38% over-all reduction in dosage, the blood urea nitrogen rose to 52.8 mg. % and the creatinine to 4.1 mg. %. This was the only patient treated by us who had to have treatment interrupted because of azotemia.

Patient 23, with cryptococcal meningitis, was not included in Table 3 because he was not treated by us but at our suggestion with amphotericin which we supplied. After 27 days of intravenous therapy with the solubilized antibiotic, he was found to have a blood urea nitrogen of 102 mg. %. Treatment was stopped, and the blood urea nitrogen fell to 35 mg. % 16 days later. Small doses of amphotericin were then given, and the blood urea nitrogen continued to fall to 12.8 mg. %.

We believe that amphotericin was a significant factor in the death of an infant (Patient 21) with congenital agammaglobulinemia. This patient was being treated for a relatively resistant (in vitro) systemic moniliasis. Therefore, we were administering large doses of the insoluble antibiotic (3 mg. per kilogram). Febrile reactions were severe. Ultimately he developed an exfoliative dermatitis which was followed by purpura and acute hepatic enlargement. He had shown brief tonic and clonic convulsive movements during the last two infusions of amphotericin. Death was attributed to overwhelming toxemia and extensive bronchopneumonia. Necropsy findings are given in his case summary.

A second patient not included in Table 3 should be mentioned briefly because of a reaction to treatment. Patient 10 was admitted in deep coma from cryptococcal meningitis. He was the first patient treated by us with intravenous amphotericin. The initial dose of 100 mg. of the suspension appeared to be well tolerated. The second daily infusion was given within two hours and was followed by a very severe chill and fever, with temperature to 112 F. His temperature fell to 100 F after 20 minutes. No detectable damage resulted from this episode of hyperthermia.

Assays have indicated a slow disappearance of solubilized amphotericin from the serum after intravenous infusion. A maximum concentration appeared in the serum 15 minutes following infusion (2.5μg. per milliliter after a dose of 0.78 mg. per kilogram of body weight) and fell rather rapidly during the first two postinfusion hours (usually to 1.0μg. per milliliter at doses of 0.5 mg. per kilogram or above). There was little or no change in the serum concentration between the second and eighth hours after infusion. The 24-hour level, in our experience, has usually been between 0.5 and 1.0μg. per milliliter of serum when the daily dose has been between 0.6 and 0.8 mg. per kilogram of body weight. One patient whose 24-hour level was 1.0μg. per milliliter had a level of 0.2μg. per milliliter 72 hours after his last infusion. Despite this persistence of low serum levels we have not found evidence of any cumulative effect when the antibiotic was given daily. Apparently, the rate of disappearance from the serum is directly proportioned to the serum concentration.

The slow disappearance of the antibiotic from the blood stream following intravenous infusion suggests the practicality of treatment on alternate days. If several days intervened between infusions, the reactions at a constant dosage were much severer than when administration was daily or every other day.

We have insufficient evidence to make any definite statement concerning the relationship of serum levels of antibiotic to azotemia. However, one patient (Patient 16), whose azotemia gradually increased over a period of seven days with a blood urea nitrogen above 30 mg. % for the last 18 days of treatment, had a low serum level (0.2μg. per milliliter) 24 hours after infusion of 0.5 mg. per kilogram of body weight. There was no detectable amphotericin in his serum 72 hours after therapy was stopped despite a blood urea nitrogen level of 52.8 mg. % and a creatinine of 4.1 mg. %.

Results of Treatment of Histoplasmosis

Four patients with histoplasmosis were treated with amphotericin B. Table 4 presents the essential data. Patient 1, with primary pulmonary disease, was treated for 164 days with oral amphotericin. Serial

TABLE 4.—*Treatment of Histoplasmosis with Amphotericin B* *

Patient	Age	Classification of Disease	Duration of Treatment, Days	Average Daily Dosage, Mg/Kg.	Response
1	7	Moderately severe primary	164 oral	90.	No definite
2	32	Reinfection, moderate	15 I. V.	1.25 (I)	Prompt improvement
			15 I. V. (q. 3d.)	1.25 (I)	Prompt improvement
			50 oral	100.	
			86 I. V.	0.37 (S)	Prompt complete healing
3	58	Chronic progressive	70 I. V.	0.87 (I)	Prompt complete healing
			8 I. V.	0.57 (S)	
			90 oral	66.	
4	45	Chronic progressive	79 I. V.	0.63 (S)	Prompt complete healing

* See Table 2 for key to abbreviations.

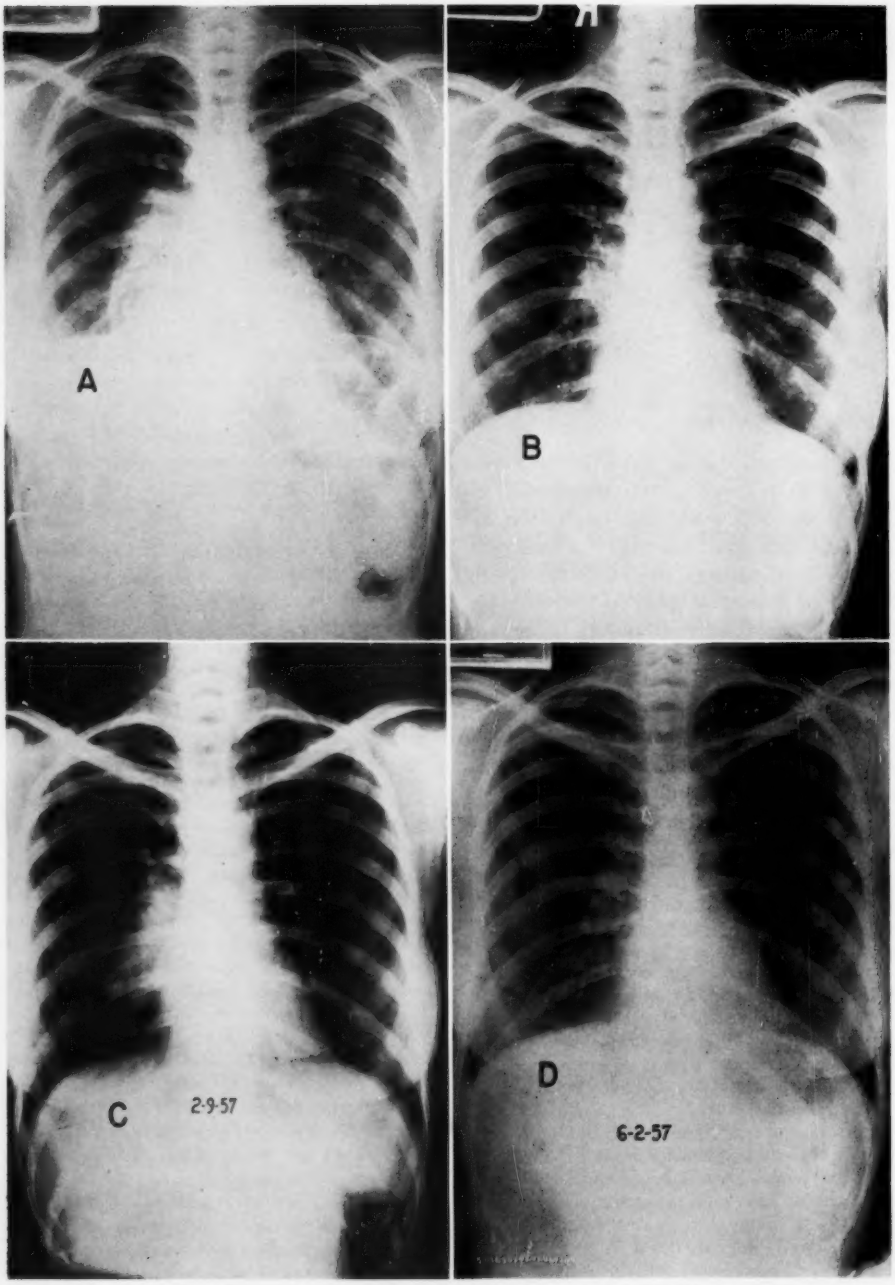
roentgenograms during and after treatment showed no evidence of any therapeutic effect of the oral antibiotic. Regression did not begin until some months after treatment.

The three patients treated intravenously responded promptly and completely. Patient 2 is particularly interesting because of her quick improvement and equally early relapse following short courses of intravenous therapy. Healing was complete after a final course of 90 days. The Figure illustrates the response of her pulmonary disease to the first and third treatments. Short abstracts of the illness of each patient follow.

PATIENT 1.—A 7-year-old girl had an insidious onset of cough and increasing fatigability in the autumn of 1956. In November a chest roentgenogram revealed infiltration in the right lung. Her respiratory symptoms worsened, and low-grade daily fever appeared in February, 1957. Sputum culture was postive for *Histoplasma capsulatum*. Cervical and axillary lymphadenopathy were noted. Serial roentgenograms showed progressive enlargement of the right hilus and infiltration of the right middle lobe, culminating in partial atelectasis of the middle lobe. Tuberculin skin tests were negative; the histoplasmin, positive. Treatment with oral amphotericin was discontinued after 164 days without any x-ray evidence of therapeutic effectiveness. Regression of the primary complex began during November, 1957.

PATIENT 2.—A 32-year-old woman had a chest x-ray made in January, 1956, that revealed only calcification in the right hilus. Productive cough, right lower chest pain, general malaise, weakness, and anorexia appeared in April. Symptoms persisted into July, when a second chest x-ray revealed right hilar adenopathy with perihilar infiltration and atelectasis of the apical segment of the right lower lobe. She was treated empirically with antituberculous drugs until September, 1956. She was then reevaluated because of persistence of symptoms and some progression of the infiltrate in the right lung. A positive skin test and complement fixation titer of 1:16 with histoplasmin led to the presumptive diagnosis of histoplasmosis. Symptomatic and x-ray response to intravenous amphotericin was excellent, and treatment was discontinued after 15 days. She was discharged in October, and her symptoms recurred about Nov. 15. The roentgenographic appearance of the chest returned to its pretreatment state, and retreatment with amphotericin was started on Dec. 7. Reactions to amphotericin were so severe that only five infusions were given in a period of 15 days. X-ray improvement was again prompt, but symptomatic change was difficult to evaluate because of the reactions to the antibiotic. She was then referred to Charity Hospital. Examination revealed a 25 lb. loss in weight, cervical lymphadenopathy, and a complement fixation titer of 1:32 with histoplasmin. The sputum contained many Gram-negative organisms and Candida. We were unable to isolate Histoplasma. Treatment resulted in prompt and complete regression of disease. Her complement fixation with histoplasmin was 1:8 at the conclusion of treatment. The Figure shows the chest x-rays.

PATIENT 3.—A 58-year-old man developed progressive ulcerative and granulomatous involvement of the posterior half of his tongue in 1954. A diagnosis of histoplasmosis was made by biopsy, and he was treated with intravenous β-diethylaminoethyl fencholate. He remained symptomatic and slowly lost weight until two months prior to his admission to Charity Hospital, in October, 1956. At the time of admission the posterior one-third of the tongue was involved by an ulcerative and



Case 2, with pulmonary histoplasmosis. *A*, chest x-ray three days prior to first course of intravenous amphotericin. Hilar adenopathy, segmental atelectasis, and pulmonary infiltration were present. *B*, x-ray appearance two weeks after first course. Infiltration and atelectasis have disappeared. *C*, this chest x-ray was made three days before the third course of amphotericin. Infiltration and segmental atelectasis have reappeared. *D*, roentgenographic appearance two weeks after third course of treatment. Only calcific hilar adenopathy remains.

granulomatous process which extended onto the anterior faucial pillars and the uvula and deeply into the midline of the hard palate and onto the alveolar ridges. The epiglottis was extensively involved, as were the pyriform fossae. Cervical lymph nodes were enlarged and tender; hepatomegaly and splenomegaly were present. Intradermal tests with histoplasmin, blastomycin, coccidioidin, and first-strength P. P. D. were negative. H. capsulatum was isolated by culture and animal inoculation from the palatal lesions. The complement-fixation titer with histoplasmin was 1:64. Treatment with amphotericin was started on Oct. 13, 1956, and by the 25th of the same month superficial epithelization of the lesions had occurred. Cervical lymph nodes, liver, and spleen were no longer palpable in January, 1957, when he was discharged and followed at intervals. He was last seen in April, 1958, at which time he remained completely healed.

PATIENT 4.—A 45-year-old man developed malaise and low-grade fever for several weeks in August, 1955. Fatigability, productive cough, and malaise appeared in April, 1956, and continued until October of the same year, when he became acutely febrile. A chest roentgenogram revealed infiltration in the left upper lobe. Treatment with numerous antibiotics was ineffectual and accompanied by a 22 lb. weight loss. A second-strength P. P. D. skin test was negative, but the histoplasmin was postive. In January, 1957, an exploratory left thoracotomy with lung biopsy was performed. The patient was told that this revealed a chronic granuloma but neither neoplasm nor tuberculosis. In April, 1957, a second acute episode occurred during spread of the disease to the right lung. Numerous sputum cultures were negative for fungi and Mycobacterium tuberculosis. Antituberculous therapy was started in June, 1957, and continued until his admission to Charity Hospital in October, 1957. At admission he was found to have bilateral apical cavitation, hepatomegaly, and axillary lymphadenopathy. Histoplasmin complement-fixation titer was 1:256. Washings from the left apical cavity were positive for H. Capsulatum by culture, animal inoculation, and direct staining. Treatment with amphotericin was terminated on Feb. 2, 1958, and a left upper lobectomy was done the following day. The wall of the cavity was very thin, shiny, and free from exudate. Microscopically it consisted of fibrous connective tissue without any evidence of inflammation in the wall or the adjacent lung. No granulomatous tissue was present. A large satellite nodule was bisected, revealing central caseation necrosis. Cultures and animal inoculation of the triturated material from one-half of the nodule were negative for Histoplasma and Mycobacterium. A most unexpected finding was the absence of any organisms when special stains were applied to sections of the other half of the nodule. Other nodules in the lung were likewise negative histologically for evidence of histoplasmosis. The right lung had cleared well by x-ray during treatment, although some fibrosis and several nodules remained. The complement-fixation titer at the conclusion of treatment was 1:32 with histoplasmin. When last seen, April 25, 1958, he was entirely well.

PATIENT 22.—Amphotericin, and suggestions for its use, were supplied by us for treatment of an additional patient with histoplasmosis. Not being directly under our care, he is not included in Table 4. The patient, an elderly man, was under treatment in a neighboring sanitorium for pulmonary tuber-

TABLE 5.—*Treatment of Blastomycosis with Amphotericin B* *

Patient	Age	Clinical Status Before Treatment	Duration of Treatment, Days	Average Daily Dosage, Mg/Kg.	Response
5	76	Disseminated; moribund	26 I. M.	1.0 (S)	None
			58 I. V.	0.65 (S)	Promptly improved
6	46	Disseminated; cachectic	Approx. 90 oral	55.0	Good, incomplete
			6 I. V.	0.92 (I)	Good, relapse
			12 I. V.	0.46 (I)	Improved
			8 I. V.	0.92 (I)	Improved
			6 I. V.	1.4 (I)	Relapsed
			90 I. V.	0.62 (S)	Complete healing
7	57	Disseminated; cachectic	20 oral 78 I. V.	83.3 1.25 (I)	Prompt complete healing
8	37	Involvement of mediastinum & questionably liver; ambulatory	43 I. M.	0.7 (S)	No way to evaluate
9	69	Disseminated; severely ill	62 I. V.	0.43 (S)	Prompt complete healing

* See Table 2 for key to abbreviations.

culosis, diabetes, and gangrene of the toes. He complained of hoarseness and dysphagia. An ulcerative and granulomatous lesion of the right vocal cord was discovered. A histological diagnosis of histoplasmosis was made. The lesion healed after treatment with intravenous amphotericin for two months.

Results of Treatment of Blastomycosis

In our experience, clinical response of North American blastomycosis to treatment with amphotericin parallels the extreme sensitivity of the organism in vitro. Oral administration may be followed by healing in some patients, but this route is not reliable, a fact well illustrated by Patient 6.

The important factors in the treatment of five patients with North American blastomycosis are in Table 5. A brief abstract of each case follows.

PATIENT 5.—A 76-year-old man complained of exertional dyspnea and easy fatigability in 1946. In 1954 his symptoms worsened and a productive cough appeared, but it was prostatism that necessitated hospitalization. After suprapubic prostatectomy a chest roentgenogram was taken. This was said to reveal far advanced bilateral pulmonary tuberculosis. He was transferred to another hospital, where the diagnosis could not be confirmed, and he was discharged. In the year prior to admission to Charity Hospital he had lost 30 lb. There was no history of chills, fever, or night sweats. During the year prior to admission he experienced periodic episodes of cyanosis during paroxysms of coughing. In December, 1956, a purulent and granulomatous lesion appeared on the distal interphalangeal joint of one finger. In the spring of 1957 cutaneous lesions appeared over the bridge of his nose and in the right eyebrow. He was admitted to Charity Hospital on Oct. 9, 1957, in acute respiratory distress. A diagnosis of blastomycosis was made by direct examination, culture, and animal inoculation of the sputum and skin scrapings. All fungal and tuberculin skin tests were negative. He required nasal oxygen throughout the early weeks of hospitalization. Because of his precarious condition, it was decided to treat him with intramuscular amphotericin in order to avoid reactions. There was no change in the appearance or mycology of the cutaneous lesions and sputum during 26 days of intramuscular treatment. Intravenous therapy was then substituted and was followed by a prompt and gratifying response. Skin lesions healed; his sputum became negative, and he began to gain weight. Just prior to the planned cessation of treatment he developed an unrecognized staphylococcal pneumonia, of which he soon died. Necropsy revealed bilateral hemorrhagic and purulent pneumonia. The large apical cavity in the left lung had a smooth and glistening lining free from exudate. Blocks of lung tissue, hilar and mediastinal lymph nodes, and bronchial exudate were negative for Blastomyces dermatitidis by culture.

PATIENT 6.—A 46-year-old man first suffered from cutaneous blastomycosis in December, 1954. Infection became systemic in 1956. Initial treatment with iodides was followed by brief healing. Relapse was treated by several courses of hydroxystilbamidine until his organism became resistant to the drug. Oral amphotericin was started in July, 1956, and continued for approximately three months at a relatively low dosage. The response was excellent but incomplete. Viable organisms could be found in areas of skin which appeared to be healed. Short courses of intravenous therapy were always followed by cutaneous relapse. This intermittent treatment had no detectable effect upon the pulmonary disease, which was first noted in May, 1956, and which slowly progressed thereafter. Upon admission, in January, 1958, he had recurrent facial, faucial, and lingual lesions. In addition the process had extended to involve the pharynx, hypopharynx, and larynx. The pulmonary disease was extensive but not massive in any area. His organism was still very sensitive to amphotericin, and all visible lesions healed during 90 days of treatment. There was considerable clearing of the pulmonary infiltration, but many of the involved areas appeared to be undergoing fibrosis.

PATIENT 7.—A 57-year-old man developed symptoms of a respiratory infection in December, 1954. A weight loss of 48 lb. and hemoptysis for three days prompted him to consult a physician. A lesion in the right lung was thought to be carcinoma, and pneumonectomy was performed on Jan. 5, 1955. The pathologist reported blastomycosis only. During the following year he failed to gain weight and developed an abscess and periostitis of the left tibia, and in September, 1955, his respiratory symptoms returned. In April, 1956, the right anterior chest wall became involved, and incision and drainage was followed by a granuloma pyogenicum. After this he was referred to Charity Hospital. At the time of admission, in August, 1956, he was tachypneic, emaciated, and lethargic and weighed 97 lb. There was an extensive blastomycotic osteochondritis and soft-tissue involvement of the right anterior thorax. Blastomycotic empyema was also present. A catheter passed into the mouth of one of the chest wall sinuses followed a broad subcutaneous space downward and laterally, both into the axilla and close to the lower costal margin anteriorly. Contrast studies with propyliodone failed to reveal any

communication with the pleural space, and no air was present above the empyema. Healing was rapid during treatment with intravenous and intrapleural amphotericin. Biopsy of the skin over the healed sinuses was negative culturally and histologically for Blastomyces prior to discharge in December, 1956. By May, 1957, he had normal exercise tolerance and a weight of 149 lb. He was last seen in April, 1958, still without evidence of blastomycosis.

PATIENT 8.—This 37-year-old woman is of little interest to this study. In the spring of 1955 she developed chest pain, weight loss, low-grade fever, and fatigability. Some months later a chest x-ray was interpreted as showing exudative and productive infiltration in the right upper lobe, with cavitation. She was treated for 15 months with antituberculous chemotherapy without improvement and was then hopitalized because of increased cavitation. A difficult right upper lobectomy was performed in June, 1957. There was extensive fibrosis and calcification, the superior vena cava being almost completely obstructed by a calcified mass. On palpation through the diaphragm, the liver was noted to be extremely firm and to contain nodules. The surgeon considered the findings at operation atypical for tuberculosis and submitted the fresh specimen for culture as well as histopathology. Fibrosing granulomatous lesions of the lung with multiple areas of cavitation were present, as well as bronchiectasis and granulomatous occlusion of large bronchi. No acid-fast bacilli were found, but animal inoculation was positive for B. dermatitidis. She had biochemical evidence of liver damage. Because much of the calcific and fibrotic disease around the superior vena cava and azygos vein had to be left within the chest, she was referred to us for medical treatment. She was afebrile and completely asymptomatic except for mild icterus. We believed it would be impossible to evaluate results of treatment. Therefore, she was given intramuscular amphotericin. There has been no evidence of recurrent blastomycosis to date.

PATIENT 9.—A 69-year-old man was discovered to have a positive serological test for syphilis in April, 1957. Immediately following treatment with penicillin there appeared joint pains, low-grade fever, arthritis, and multiple purpuric lesions over the arms and legs. His temperature increased to between 100 and 102 F each day. Weight loss and pallor were progressive. The halluces and the interphalangeal joint of the right third finger became abscessed. Aspiration of these lesions and the hemorrhagic deep skin lesions revealed B. dermatitidis on direct examination and culture. B. dermatitidis was isolated from the urinary sediment also. The left fifth finger was amputated because of extensive osteomyelitic destruction and ulceration. At the conclusion of treatment, in September, 1957, findings on biospy of residual areas of pigmentation were negative on culture and histologically for Blastomyces. As of April, 1958, no further evidence of blastomycosis has appeared.

Results of Treatment of Cryptococcosis

Cryptococcosis is one of the commoner deep mycoses in Louisiana. In the past, all patients with central nervous system involvement died from their disease, but a few pursued a remittent type of illness for several years. Consequently, follow-up of at least five years will be necessary before one can estimate the curative effect of a therapeutic agent. Our experience has included a sufficient number of critically ill patients to permit definite statements about the immediate effectiveness of amphotericin. Only two of our patients have died, one of whom was treated for only four days; the second refused therapy after the 14th infusion. Two have been observed for a full year after termination of intravenous therapy. Both are fully ambulatory and pursuing their ordinary activities without symptoms.

Patient 15 is of considerable interest because of involvement of the skin and scalp which could be observed. During intravenous amphotericin therapy the skin lesions improved considerably. However, healing was far from complete at the time oral amphotericin was substituted for the intravenous antibiotic. The observable lesions rapidly approached their appearance at the time of admission during oral treatment.

The changes in the spinal fluid of patients with cryptococcal meningitis were not as encouraging as those reported by Lehan, et al.[4] They reported normalization of the fluid in four of five patients. Spinal fluid glucose rose rather rapidly in our patients after the institution of intravenous treatment. Only one patient has had a return to normal of both spinal fluid protein and cellularity. This patient (Patient 14) had normal spinal fluid findings four months after treatment was terminated.

Patient 11, whose maximum spinal fluid protein was 324 mg. % during treatment, still had a level of 97 mg. % 10 months after cessation of therapy; the spinal fluid cell count was normal. Patient 12, who had 450 mg. % of protein in her spinal fluid during treatment, had a level of 97 mg. % 10 months after the end of intravenous therapy. One patient who is still under treatment, Patient 16, entered with acutely progressive disease. Although his spinal fluid glucose was very low, the protein was only 58 mg. %. During the course of 59 days of combined intravenous and intrathecal therapy the protein remained below this level and was within normal limits when treatment was interrupted because of azotemia. It is of speculative interest that this patient had no detectable amphotericin in the spinal fluid 24 hours after intravenous infusion and 72 hours after intrathecal infection and was the only patient to show persistence of cryptococci beyond the second week of treatment. He had many cryptococci in his spinal fluid after 59 intravenous infusions and 17 intrathecal instillations of amphotericin. We were unable to culture these cryptococci after 14 days of treatment. His sudden improvement after initial worsening occurred when intrathecal therapy was started. This may have been coincidental.

The essentials of treatment of each patient are in Table 6. An abstract of each case is given in the succeeding paragraphs.

PATIENT 10.—A 67-year-old man had an acute onset of headache with episodes of confusion in March, 1956. Cryptococci were found by smear, culture, and animal inoculation of his spinal fluid. Personality changes, mental impairment, and a transient right hemiplegia were observed early in his illness. He was discharged from hospital on

TABLE 6.—*Treatment of Cryptococcosis with Amphotericin B* *

Patient	Age	Clinical Status Before Treatment	Involvement	Treatment, Days	Average Daily Dosage Mg/Kg.	Clinical Response
10	67	Comatose, moribund	CNS, adrenals, kidneys	3 oral 4 I. V.	80. 1.66 (I)	Died
11	43	Semicomatose, delirious, poor	CNS	34 oral 115 I. V. 96 I. V. 60 I. M.	68. 1.07 (I) 0.35 (S) 0.28 (S)	Promptly improved; working full time; 1 yr. post therapy
12	52	Comatose, poor	CNS	20 I. V. 88 I. V. 74 I. V.(q. o. d.) 90 I. M.(q. o. d.)	1.0 (I) 0.54 (S) 0.54 (S) 0.31 (S)	Promptly improved; full activity, 1 yr. post intravenous treatment
13	63	Ambulatory, good	CNS	90 I. M. Twice weekly I. T. (14) 90 I. V. I. T. twice	0.82 (S) 0.57 (S)	Improved More improvement
14	34	Good, ambulatory	CNS	56 I. V. Twice weekly I. T. (11) 100 I. M.	1.0 (S) 0.47 (S)	Promptly improved; full activity 9 mo. post intravenous treatment
15	72	Fair, ambulatory	Skin, bone, lungs, liver, spleen, CNS	14 I. V. 26 oral	0.75 (I) 50.	Improved on intravenous treatment, worsened during oral treatment; died
16	15	Acutely ill, delirious	CNS	59 I. V. Twice weekly I. T. (17) Course 2 †	0.70 (S)	Promptly improved with I. V. & I. T. therapy.

* See Table 2 for key to abbreviations.
† Being given at time of writing.

treatment with a sulfonamide. During June, 1956, he became comatose and unresponsive and was admitted to Charity Hospital. His spinal fluid was under grossly increased pressure and contained 13 mg. % of glucose, 42 mg. % of protein, and innumerable cryptococci. Suspension of amphotericin B powder in sodium lauryl sulfate was given by Levin tube in a dosage of 400 mg. every two hours. Intravenous suspension of amphotericin was started at the same time. He died early in the morning of the sixth hospital day, without any apparent improvement. Necropsy revealed cryptococcal meningitis, encephalitis, and cryptococcosis of the adrenal and kidneys.

PATIENT 11.—A 43-year-old man had the sudden onset of headache and fever in August, 1956. Within 20 days he was irrational and showed evidence of meningitis. The diagnosis of cryptococcosis was made by direct and cultural examination of the spinal fluid before he was transferred to Charity Hospital. At the time of admission he was disoriented and irrational but responded to stimulation. His temperature was 102 F and his respirations 13 per minute. Many cryptococci were present in the spinal fluid, and these were isolated by culture and animal inoculation. Response to intravenous administration of the insoluble suspension of amphortericin was excellent. Pancreatic deoxyribonuclease was given intrathecally in a dosage of 200,000 units per injection for several days. His sensorium cleared remarkably within one week, and after two months of treatment he was fully ambulatory. Intravenous therapy was maintained for slightly more than six months, and intramuscular treatment was given for an additional two months. He has remained well during the first year of post-treatment observation.

PATIENT 12.—A 52-year-old woman had the abrupt onset of roaring tinnitus and impaired consciousness in September, 1955. She was observed to be ataxic and to have external divergence of the right eye. Headache and diplopia led to hospitalization. Papilledema was present, but ventriculography was normal. The spinal fluid was not examined. She was discharged with a diagnosis of "cerebral vasospasm." One year later she complained of anorexia, periodic nausea and vomiting, and suprapubic discomfort. Urinary retention was found. Her behavior was abnormal, with periods of disorientation. She became febrile, unable to walk, and finally semicomatose. There was temporal pallor of both optic disks, a loss of motor power and tendon reflexes in the lower extremities, and intention tremor in the upper extremities. Cryptococci were found by direct examination, animal inoculation, and culture of the spinal fluid. Her response to treatment with amphotericin was excellent but complicated by frequent thrombophlebitis. Intravenous therapy was given for six months, a part of the time on alternate days. She has remained well and fully ambulatory during a year of observation after discontinuation of intravenous treatment.

PATIENT 13.—A 63-year-old man had a gradual onset of weakness of the lower extremities. He was observed to have impaired recent memory and Parkinsonian tremor in September, 1955. He soon exhibited intermittent ataxia and urinary dribbling. Repeated spinal fluid examinations revealed pleocytosis, low sugar, and high protein but were otherwise negative. In November, 1956, fluid obtained at pneumoencephalography was positive for Cryptococcus neoformans pathogenic for mice. He received amphotericin intravenously for 3 days and orally for 30 days. He became discouraged and rejected further treatment. There was no alteration in his spinal fluid following this period of treatment. Because of increasing memory impairment and ataxia, he was admitted to Charity Hospital in September, 1957. Cryptococci were found in the spinal fluid by direct examination, culture, and animal inoculation. Semiweekly intrathecal therapy and daily intramuscular amphotericin were well tolerated. The spinal fluid became negative for Cryptococcus within the first week. He was discharged for observation after three months of treatment. Since we became convinced of the ineffectiveness of intramuscular amphotericin during his first month at home, he was recalled for intravenous treatment in January, 1958. At readmission the spinal fluid contained 24 leukocytes, a quantitative protein of 202 mg. %, glucose of 63 mg. %, but no cryptococci. Two daily intrathecal administrations of 1 mg. of amphotericin were given before any intravenous therapy was started. On the following day the spinal fluid protein was only 122 mg. %. Because of his age and cardiovascular disease, only three months of intravenous treatment were given. Improvement was much more definite following intravenous treatment. Intrathecal therapy was given only on the two successive days during his second hospitalization. Following the second instillation of 1 mg. of amphotericin he developed transient paresis of the left lower extremity, which subsided within 72 hours. He will be observed at three-month intervals.

PATIENT 14.—A 34-year-old woman experienced the onset of a steady frontal headache accompanied by nausea during the first week of March, 1957. Symptoms persisted and were accompanied by vomiting and low-grade fever. The appearance of meningismus prompted examination of the spinal fluid, which was abnormal. Muscular weakness and increasing fever led to admission to Charity Hospital. The spinal fluid was positive by culture for C. neoformans on two occasions. Treatment with both intravenous and intrathecal ampho-

tericin was given for a period of two months. The intrathecal antibiotic regularly produced some paresthesias in the crural areas and both legs. There was no true pain. Intramuscular treatment was given for more than three months after the termination of intravenous therapy. She has remained completely well during the nine months since intravenous treatment was stopped.

PATIENT 15.—A 72-year-old man became aware of a small growth on his scalp in May, 1956. This was diagnosed as an epithelioma without biopsy and treated by roentgen irradiation. The lesion continued to spread, and peripheral lesions appeared. Antibiotics did not alter their appearance. A biopsy done on Oct. 22, 1956, was reported as showing histoplasmosis. Various therapeutic agents were used, but the lesion progressed, and new ones appeared over the scalp, arm, and chest. He began to lose weight, and the lesions on the scalp became quite painful. Since he also had angina pectoris, bronchial asthma, emphysema, and a previous myocardial infarction, hospitalization was advised. At the time of admission there were large crusted lesions over the entire vertex of the scalp and a central ulcer crater involving the periostium of the calvaria. Acneform lesions were present over the chest and right forearm. Bilateral bronchopneumonic infiltration was seen by x-ray. Biopsies of the skin and scalp lesions revealed C. neoformans histologically and by culture. The cerebrospinal fluid protein was 92 mg. %, but neither organisms nor cells were seen. There was biochemical evidence of liver dysfunction. He refused intravenous medication after the 14th infusion and worsened under oral treatment. He died six months later with cryptococcosis of the scalp, chest, forearm, lungs, liver, and spleen.

PATIENT 16.—A 15-year-old schoolboy experienced the abrupt onset of nausea and vomiting on Jan. 19, 1958. On Jan. 24, he became febrile and complained of severe headache and a stiff neck. The presence of meningitis was confirmed on Jan. 29, and C. neoformans was found in the spinal fluid by Feb. 7. He was admitted to Charity Hospital on Feb. 9, acutely ill with marked meningitis. There was bilateral papilledema, irrationality, and delirium. More cryptococci than lymphocytes were present in the spinal fluid, which was under greatly increased pressure. During the first five days of intravenous amphotericin his symptoms not only persisted but worsened and he had to be restrained. He then began to respond to treatment very rapidly and soon to gain weight. After he had become fully ambulatory, treatment was interrupted because of azotemia. After an interval of four weeks without treatment, cryptococci could not be found in his spinal fluid, whereas they were still present, but not culturable, at the time treatment was interrupted. A second course of treatment was complicated by the reappearance of azotemia, even though intravenous amphotericin was given on alternate days in a dosage of 0.47 mg. per kilogram of body weight. Intravenous treatment was interrupted for the second time.

PATIENT 23.—This patient is not included in Table 6 because he was not directly under our care. A man aged 57 had a sudden onset of low-grade meningitis. Because of the appearance of signs of parenchymal invasion, a pneumoencephalogram and later a ventriculogram were done. Obstruction along the base of the brain was demonstrated, and the fluid removed was culturally positive for C. neoformans. Continuous ventricular drainage was instituted. His condition was considered "extremely grave" at the time amphotericin was started. The solubilized form was given intrathecally and intravenously. Intravenous dosage was increased from 12.5 mg. to 50 mg. over a period of 12 days. Fifty milligrams of amphotericin was given intravenously daily for the next 15 days, at which time he was found to have a blood urea nitrogen of 102 mg. %. Treatment was stopped until the blood urea nitrogen had fallen to 35 mg. %, 16 days later. Amphotericin was then resumed in small doses and very gradually increased. The blood urea nitrogen continued to fall and was 12.8 mg. % 27 days after it had been 102 mg. %. He died suddenly without having shown any certain improvement while under treatment.

Results of Treatment of Miscellaneous Deep Mycoses

Moniliasis, sporotrichosis and coccidioidomycosis have been encountered too infrequently during this study to warrant separate tabulation. This group of patients is summarized in Table 7.

Two patients with moniliasis have been treated with intravenous amphotericin B. Both patients had positive blood cultures, which became negative promptly after treatment was started. It is not possible to evaluate the effectiveness of amphotericin in either patient, other than its immediate activity. Systemic moniliasis occurring in a congenitally agammaglobulinemic infant severely tests any therapeutic agent. The fact that necropsy revealed sterilization of the numerous small liver abscesses and an absence of Candida from the diffusely involved lungs suggest candicidal activity in such a patient even though oral thrush per-

TABLE 7.—*Treatment of Miscellaneous Deep Mycoses with Amphotericin B* *

Patient	Age	Diagnosis	Clinical Status Before Treatment	Treatment, Days	Average Daily Dose, Mg/Kg.	Response
17	35	Disseminated coccidioidomycosis	Moribund	66 I. V.	3.0 (I)	Remarkably improved at high dosage; became ambulatory; gradual relapse at lower dosage & during "vacation" of 38 days
				20 oral	242.0	
				113 I. V.	1.5 (I)	
				65 I. V.	0.6 (S)	
				88 I. V.	0.43 (S)	
				48 I. V. q. o. d.	0.43 (S)	
				Course 2 †		Stabilized; sudden deterioration & death
				18 I. V.	0.6 (S)	
				65 I. V.	1.0 (S)	
				34 I. V.	1.14 (S)	
18	61	Disseminated sporotrichosis	Cachectic, severely impaired gait	58 I. V.	0.63 (S)	Prompt complete healing, normal gait
19	30	Sporotrichosis	Good	49 I. V.	0.42 (S)	Good; complete healing.
20	62	Moniliasis (pyelonephritis)	Poor, uremic	6 I. V.	0.25 (S)	Fever abated; blood & urine cultures became negative; died abruptly
21	6 mo.	Moniliasis	Poor, congenital agammaglobulinemia	13 I. V.	2.0 (I)	Blood cultures became negative; thrush persisted; died
				13 I. V.	3.0 (I)	

* See Table 2 for key to abbreviations.

† Course 2 was separated from Course 1 by 38 days at home and treatment with intravenous eulicin between Sept. 3 and Oct. 31, 1957.

sisted. The second patient, with evidence of systemic moniliasis superimposed on chronic pyelonephritis, presented a much more difficult problem for evaluation. The abstracts of the hospital records indicate our dilemma.

PATIENT 21.—A 6-month-old boy developed normally until age 4 months, when he developed furunculosis. Antibiotic therapy and incision resulted in improvement but not complete healing. During the course of antibiotic therapy oral thrush developed and extended from the mouth and tongue onto the hypopharynx. The thrush improved with local application of methylrosaniline chloride (gentian violet) but could not be eliminated and did not respond to nystatin. He became more fretful and febrile. At the time of hospitalization he was febrile and had indolent furuncles on the forearm and chest and extensive thrush. Soon after admission he developed bilateral pneumonitis. The furuncles were due to a penicillin-resistant hemolytic Staphylococcus pyogenes var. aureus. These healed following appropriate antibiotic therapy. The pulmonary infiltration increased, and he remained febrile. Treatment with intravenous suspension of amphotericin B was followed by almost complete clearing of the x-ray evidence of pneumonia. Blood cultures which had been positive for Candida albicans became negative. Reactions to amphotericin were severe and appeared to be in large part responsible for the infant's death. Necropsy revealed acute bronchopneumonia together with congestion, edema, and interstitial pneumonitis. The spleen was markedly congested and had focal areas of interstitial hemorrhage and a perisplenitis. The liver was involved by many focal areas of hemorrhage with destruction of the liver cords in the vicinity. A large area of hemorrhage was present in the cortex of the adrenals. Tubular degeneration was seen in the kidneys. Cultures taken from the liver, the necrotic areas in the liver, and bronchopneumonic areas were negative for Candida. Special stains failed to reveal any organisms.

PATIENT 20.—A 62-year-old man was an obese diabetic who developed a febrile illness during August, 1957. The presence of a cardiac murmur, continued fever, and a blood culture positive for an enterococcus led to treatment for bacterial endocarditis with antibiotics. Improvement was brief, complicated by congestive failure and by the development of uremia, in October. C. albicans was recovered repeatedly from the urine during October and early November and from the blood on Nov. 4. Intravenous amphotericin was followed immediately by cessation of fever and by negative blood and urine cultures for Candida. He died abruptly on the sixth day of treatment. Autopsy revealed a severe chronic pyelonephritis but no endocarditis.

TABLE 8.—*Relationship of Spinal Fluid Protein to Spinal Fluid Amphotericin* *

Patient	Diagnosis	Daily I. V. Dosage, Mg/Kg.	Spinal Fluid Protein, Mg. %	Spinal Fluid Amphotericin, μg/Ml.	Serum Amphotericin 24 Hr. After Infusion, μg/Ml.
11	CNS Cryptococcosis	1.00 (I) 0.33 (S)	219 162	0.27 0.27	
12	CNS cryptococcosis	0.54 (S) 0.54 (S)	450 216	0.46 0.27	
13	CNS cryptococcosis	0.33 (S) 0.50 (S) 0.75 (S)	166 166 160	0.17 0.17 0.17	0.5
16	CNS cryptococcosis	0.50 (S) 0.83 (S) 0.50 (S) †	32 27 78	<0.04 <0.04 0.1	0.2
18	Sporotrichosis (no CNS disease)	0.73 (S)	25	<0.04	1.0

* See Table 2 for key to abbreviations.
† Second course of treatment.

Histologically, the kidneys were said to show mucormycosis, but no cultures were made at the time of necropsy.

Two patients with sporotrichosis have been treated with amphotericin. One was an unusual case of widely disseminated disease, whereas the other was the usual type with cutaneous and lymphatic involvement. Healing in both was prompt and complete. The response of sporotrichotic arthritis was unexpectedly prompt. The case summaries follow.

PATIENT 18.—A 61-year-old man had cut his foot 32 years prior to admission. The cut area became swollen and ulcerated and drained over a period of approximately six months. A scar remained, but he was asymptomatic until September, 1957. At this time the scar became swollen and ulcerated. Nodular ulceration appeared on his hands, arms, feet, legs, and back. These were nonpainful and raised and then became ulcerated and drained, with partial healing. During November dysphagia developed to the point of restricting his dietary to semisolids and hoarseness appeared concurrently. A 30 lb. weight loss with anemia resulted. Cervical lymph nodes became enlarged, and one group of them suppurated and were drained. Late in November he experienced painful limitation of motion of his knees, ankles, hips, and lower spine. Laryngoscopy revealed an extensive granulomatous lesion of the hypopharynx and larynx, for which he was referred to Charity Hospital. Sporotrichum schenckii was recovered by culture and animal inoculation from biopsy specimens of both the laryngeal and the subcutaneous lesions. X-rays revealed degenerative changes in the joints together with lytic bone lesions beneath some of the healing cutaneous lesions. During early hospitalization he developed a small interlobar effusion in the right lung with the appearance of a patchy bronchopneumonia in both lower lung fields. The granuloma extended upward from the hypopharynx to the faucial pillars. Intravenous amphotericin B was well tolerated. Forty-eight days after treatment was started the pharynx and larynx showed no active granulomas. His gait became normal, and he was discharged April 1, 1958.

PATIENT 19.—A 30-year-old man was bitten by "fire ants" in December, 1957. Within 36 hours the usual suppurative reaction appeared at the site of the bites. All but one of the bites healed, and this one gradually enlarged and ulcerated. The ulcer increased in size, and a chain of subcutaneous nodules appeared extending along the biceps. He was unable to straighten his arm. Axillary lymphadenopathy was also present on the involved side. Material taken from the ulcer and other material aspirated from one of the subcutaneous nodules were positive for S. schenckii by culture. Treatment with intravenous amphotericin was started in February and completed on April 2, 1958. A subcutaneous abscess was aspirated on March 4 and was culturally negative. Healing was complete at the time of discharge.

The last patient included in this group had severely disseminated coccidioidomycosis. She showed cutaneous anergy and high serum complement-fixation titer against coccidioidin throughout her illness. She was under treatment for longer than any of our patients, having received 12,250 mg. of the insoluble suspension and 6975 mg. of the solubilized antibiotic intravenously during the interval between June 27, 1956, and March 10, 1958. Her initial response to large doses of the antibiotic was most impressive. The presence of walled-off abscesses was probably the major factor in the ultimate failure of treatment. In addition, her prolonged illness and our sympathy for her led to inadequate dosage from March through July, 1957. She deteriorated noticeably during a "vacation" of 38 days outside the hospital during late summer of 1957. Eulicin, an antifungal antibiotic, was administered intravenously between Sept. 3

and Oct. 31, 1957, with what appeared to be an initial clinical improvement lasting about 10 days. However, during the course of eulicin therapy it was evident that further dissemination had occurred, with the appearance of multiple pyoarthroses. Instillation of eulicin directly into these involved joints and into fluctuant lymph nodes did not produce sterilization despite the very large amount instilled relative to the in vitro sensitivity of her Coccidioides. Instillation of large doses of solubilized amphotericin into the same areas and into other similar areas produced sterilization. It is of some importance that this patient received prolonged amphotericin treatment without any evidence of significant toxicity. The essential elements in her illness are summarized in the succeeding paragraph.

PATIENT 17.—A 35-year-old woman developed pulmonary coccidioidomycosis in October, 1955, while in Arizona. Because of persistent fever, weight loss, and malaise, she returned to Louisiana in February, 1956. At the time of admission, in March, 1956, she had daily fever, with temperature to 104 F, and severe dyspnea. Examination revealed generalized lymphadenopathy, subcutaneous nodules over the thorax, splenomegaly, hepatomegaly, bilateral pneumonitis, and tenderness of the bones of the feet. She had laboratory evidence of parenchymal liver damage. There was no cutaneous reaction to standard coccidioidin even at a dilution of 1:10. The complement-fixation titer was 1:256. Daily treatment with 337 mg. of hydroxystilbamidine was continued until mild icterus appeared, the third week of June. There was some amelioration of fever and symptoms during this course of therapy. However, the pulmonary involvement increased; she became much weaker and disoriented, and her weight decreased to less than 70 lb. As already indicated, her response to intravenous amphotericin was striking. There was reduction in the pulmonary infiltration, a clearing of a coccidioidal empyema, and very definite improvement in the extensive osteomyelitis of both feet. She became afebrile by February, 1957, began to gain weight, and became ambulatory. Sputum production decreased markedly but was culturally sterile only once during April, 1957. Viable Coccidioides immitis were present in May, 1957, and subsequently. On low dosages of amphotericin and during treatment on an every-other-day basis she gradually relapsed during early summer of 1957. After treatment with eulicin, amphotericin B was restarted in November and continued at high dosages until the day of death, March 10, 1958. She was afebrile most of the time and had no evidence of azotemia. Local treatment of osteomyelitis, suppurative arthritis, and accessible suppurative lymphadenitis was carried out successfully during this time. Necropsy demonstrated many large inaccessible abscesses containing viable Coccidioides and involvement of one adrenal.

Comment and Summary

The ultimate place of amphotericin B in the treatment of the deep mycoses must await both a longer observation of treated patients and comparison with more recently developed therapeutic agents. It is evident that this antifungal antibiotic is highly effective initially against North American blastomycosis, histoplasmosis, cryptococcosis, and sporotrichosis when it is administered intravenously. In general, it may be said to be a useful agent against most infections with yeast-like fungi.

Our experience with moniliasis and coccidioidomycosis during this study was inadequate for evaluation of the effectiveness of amphotericin B. The fact that the strain of Coccidioides immitis involved retained its initial in vitro sensitivity through more than a year of treatment is encouraging. The nature of the pathology produced by severely disseminated coccidioidomycosis makes it unlikely that any antibiotic will be curative, by itself, after large abscesses have formed.

Amphotericin B is not suitable for oral or intramuscular administration in its present form. Assays of serum drawn after intramuscular injection have failed to reveal any detectable antibiotic. Gastrointestinal absorption is poor and apparently irregular.

Intravenous administration requires careful supervision and occasionally some ingenuity in suppressing side-reactions. The toxic effects observed to date indicate that this valuable antibiotic may not be accepted by patients or physicians unless each is properly motivated and instructed. Its use should not be casual.

The intravenous administration of 0.5 mg. or more of amphotericin B per kilogram of body weight produced prolonged serum

levels, suggesting the feasibility of infusions on alternate days. Randomized cases and prolonged follow-up may be necessary to test the relative efficacy of daily and alternate-day treatment. Alternate-day treatment with a dosage of 0.47 mg. per kilogram did not prevent the reappearance of azotemia in one patient.

Solubilized amphotericin B was well tolerated and effective when injected into pus-containing serous spaces, abscesses, and suppurated lymph nodes.

One milligram of solubilized amphotericin was tolerated very well when injected slowly intrathecally if the antibiotic was preceded by 20 mg. of sodium succinate ester of hydrocortisone and if the amphotericin was well diluted with spinal fluid in the injecting syringe. Assays of the spinal fluid of two patients indicated that a significant level (0.33μg. per milliliter; 0.46μg. per milliliter) was present 24 hours after injection. A detectable level was present 48 hours after injection but absent by 72 hours. Intrathecal instillation of 1 mg. of amphotericin on two successive days produced undesirable toxic effects.

The history of treatment of meningeal infections is replete with examples of the rise and fall of intrathecal therapy. Initially deemed essential to success, it has been discarded ultimately as unnecessary and dangerous. Our present experience with the treatment of cryptococcal meningitis suggests a correlation between the spinal fluid protein level and the passage of amphotericin into the cerebrospinal fluid. The level of spinal fluid protein seemed more of a determinant than intravenous dosage. We believe that the apparent relationship between the concentrations of protein and amphotericin in the spinal fluid is a problem which must be answered before the role of intrathecal therapy can be decided. Until then we recommend the use of intrathecal amphotericin in patients with central nervous system involvement by yeast-like fungi if the spinal fluid proteins are below 100 mg. %.

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The Diagnostic Value of Punch Biopsy of the Knee Synovium

W. M. MIKKELSEN, M.D.; I. F. DUFF, M.D.; C. W. CASTOR, M.D.; H. A. ZEVELY, M.D., and A. J. FRENCH, M.D., Ann Arbor, Mich.

The technique of biopsy occupies a position of undisputed importance as a diagnostic procedure. It has not found wide application in the field of rheumatic diseases, however, because of the expense and period of incapacity involved with conventional arthrotomy. The situation was significantly improved, we believe, in 1951, when Polley and Bickel [1] described their experiences with an instrument for punch biopsy of the synovial membrane. In several subsequent reports [2-4] these authors have confirmed their opinion regarding the diagnostic value of the method. Our initial report [5] was in agreement, stating that the procedure was considered a practical diagnostic method.

The Polley-Bickel instrument (Fig. 1) is simply constructed. The main part is a hollow stainless-steel tube with a trocar point and a hooked opening on the dorsal surface near the trocar tip. A hollow tubular knife with a sharp cutting rim fits inside the outer tube and is used to sever specimens, which are manipulated into the opening on the dorsum of the outer tube. An extractor with a corkscrew-like tip is then used to remove the specimen from the lumen of the inner tube.

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From the Rackham Arthritis Research Unit and the Department of Pathology, University of Michigan. The Rackham Arthritis Research Unit is supported by a grant from the Horace H. Rackham School of Graduate Studies. The expenses of this study were defrayed in part by grants from the Michigan Chapter, Arthritis and Rheumatism Foundation, and a grant from the United States Public Health Service.

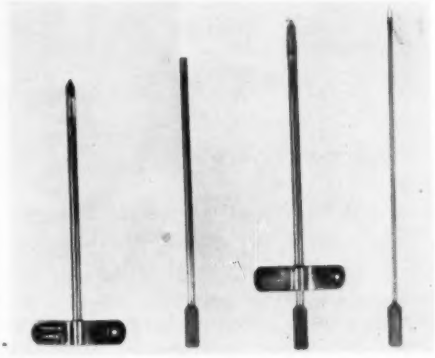

Fig. 1.—The Polley-Bickel biopsy instrument. From left to right are the outer trocar, the inner cutting knife, the trocar and knife assembled, and the corkscrew-tipped extractor. Available from V. Mueller & Co., Rochester, Minn.

In our Research Unit punch biopsy has been carried out in a standard treatment room, not uncommonly on outpatients. Strict aseptic technique is imperative, since the hazard of introducing infection exists whenever a needle is inserted into a joint. The knee joint is approached laterally or medially through the suprapatellar pouch (Fig. 2). The skin, subcutaneous tissue, and joint capsule are carefully infiltrated with 1% lidocaine (Xylocaine) solution, and the biopsy instrument is then introduced through a small stab wound. Synovial fluid is aspirated through the hollow needle and examined for cytological and physicochemical characteristics. If there is no appreciable effusion, distention of the synovial space with 30 to 50 ml. of isotonic saline solution may facilitate introduction of the instrument. About four specimens are then obtained from divergent areas of the synovial space and fixed immediately in 10%

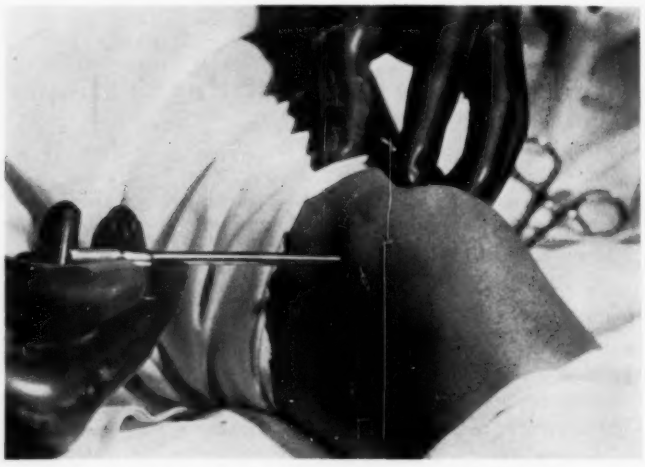

Fig. 2.—View of the biopsy instrument in place. The surgeon's left index finger is on the superior margin of the patella. (Reproduced by permission from *American Journal of Medicine* 20:510, 1956.)

formalin. Specimens are prepared in the routine manner and stained with hematoxylin and eosin. The procedure is well tolerated and relatively painless. Patients are permitted to walk immediately after the procedure but are requested to avoid any unnecessary activity for 24 hours.

Diagnostic Value of Punch Synovial Biopsy

This technique has been employed to obtain synovial tissue from the knees of 190 patients on 207 occasions. The incidence of failure to obtain synovial tissue has been about 5%. Ability to obtain satisfactory material has been definitely improved by experience. Complications have been few, consisting of mild transient hemarthrosis and superficial thrombophlebitis in two instances each. In no case could intra-articular infection be attributed to punch biopsy.

The diagnostic value of the procedure has been carefully studied (Table) and correlated with pertinent clinical and laboratory information. Punch biopsy was considered of definite diagnostic aid in 77 cases (40% of the group of 190 patients). In 99 cases (53%) synovial changes were either absent, too slight, or too nonspecific to suggest a definite diagnosis. In only four instances (2%) was an incorrect diagnosis suggested by the procedure.

Diagnostic Value of Punch Synovial Biopsy in 190 Patients

	No.	%
Of definite diagnostic aid	77	40
Changes absent, too slight, or too nonspecific to be of aid	99	53
Misleading	4	2
Technical failures	10	5

Rheumatoid Arthritis

Synovial biopsy was performed on 71 occasions where the diagnosis of definite rheumatoid arthritis was warranted on the basis of the tentative criteria of the American Rheumatism Association.[6] Synovial characteristics were considered compatible with the clinical diagnosis in 40 cases (56%). Changes encountered with some frequency included (1) fibrinous or fibrinopurulent exudate on the synovial surface; (2) hyperplasia of the synovial intimal cells; (3) edema; (4) fibroblastic proliferation throughout the synovial tissue; (5) "homogenization" of collagen fibers; (6) inflammatory-cell infiltration, predominently lymphocytic and plasmocytic, often most marked in perivascular areas and occasionally forming follicle-like collections, and (7) vascular changes, including increase in number of vessels, congestion, and thickening of vessel walls. Occasional "palisading" of synovial cells was apparent, but lesions

Fig. 3 (Case 1).—Section through a synovial villus. There is minimal hyperplasia of the synovial cells. In the subsynovium there is marked congestion and edema, with a heavy infiltration of mononuclear inflammatory cells with some focal collections. Changes considered characteristic of rheumatoid arthritis. Hematoxylin and eosin; reduced 10% from mag. × 90.

strongly reminiscent of the rheumatoid nodule were rarely observed. No single finding or combination thereof was considered diagnostic of rheumatoid arthritis. It was not possible to correlate the synovial appearance with the duration, stage of progression, or activity of the rheumatoid process. The severity of synovial abnormality likewise appeared to be independent of the degree of impairment of synovial fluid viscosity or mucin clot formation and of the results of the sensitized sheep-cell agglutination test. No essential differences in synovial morphology were found between rheumatoid arthritis and the following conditions: juvenile rheumatoid arthritis, peripheral joint involvement in rheumatoid spondylitis, Reiter's syndrome, and apparent rheumatoid arthritis associated with positive L. E.-cell preparations, psoriasis, or Sjögren's syndrome.

Case 1 (Fig. 3).—This 12-year-old schoolgirl had developed a spontaneous effusion of the right knee six months previously. There had been no other joint involvement and no systemic symptoms. Physical examination was negative except for the presence of a moderate effusion of the right knee. Synovial fluid contained 4650 leukocytes per cubic millimeter, of which 71% were polymorphonuclear cells; mucin clot formation was poor, and the viscosity was very low. The most probable diagnoses were considered to be monarticular rheumatoid arthritis or specific infectious arthritis, particularly tuberculosis. Examination of synovial tissue obtained by punch biopsy revealed moderate hyperplasia of the synovial lining cells, occasional areas of superficial ulceration and adherent fibrin, and a heavy subsynovial inflammatory-cell infiltrate, mostly plasma cells and lymphocytes, with occasional lymphoid aggregates. These changes were considered consistent with the diagnosis of rheumatoid arthritis, which was

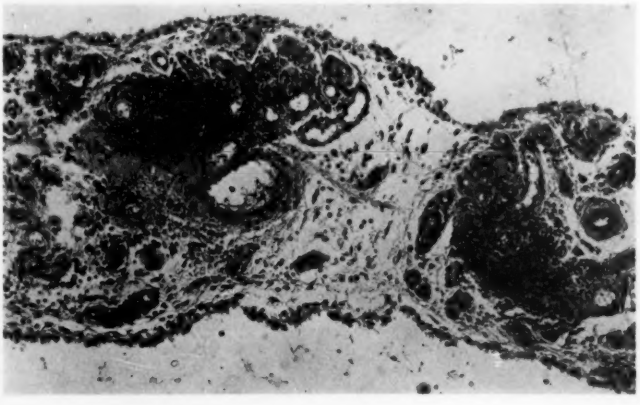

Fig. 4 (Case 2).—In this section through synovial tissue there is essentially no reduplication of the synovial-cell layer. In the subsynovial tissue there is edema and scattered perivascular and focal collections of inflammatory cells, mostly lymphocytes and plasma cells. Changes considered compatible with rheumatoid arthritis. Hematoxylin and eosin; reduced 10% from mag. × 140.

further suggested by sensitized sheep-cell agglutination test (Ziff method) positive in 1:56 dilution.

CASE 2 (Fig. 4).—This 61-year-old schoolteacher had experienced intermittent episodes of arthritis, usually involving one or several peripheral joints, over a period of 18 months. There had been no persistent or residual joint change. Physical examination disclosed evidence of moderately active synovitis in the right wrist and left knee. The serum urate level was 6.5 mg. %. Synovial fluid nucleated-cell count was 7350 per cubic millimeter, of which 39% were polymorphonuclear forms; mucin clot formation was poor, and the relative viscosity very low. The synovium showed a villous structure, with some hyperplasia of the synovial intimal cells; in the subsynovium were scattered heavy collections of lymphocytes, with some plasma cells and eosinophils, with formation of early follicles. No urate deposits were observed, and the changes were considered compatible with the diagnosis of rheumatoid arthritis. The patient has subsequently developed a generalized polyarthritis characteristic of rheumatoid arthritis; the sensitized sheep-cell agglutination test is positive in a titer greater than 1:56.

Other Connective Tissue Diseases

Inflammatory changes were sometimes present in cases of rheumatic fever, serum sickness, systemic lupus erythematosus, dermatomyositis, scleroderma, and polyarteritis nodosa. Unfortunately, findings were often minimal and so similar qualitatively that synovial biopsy did not serve to differentiate these conditions from each other or from rheumatoid arthritis.

Osteoarthritis

Punch biopsy was performed in eight cases where the clinical diagnosis was osteoarthritis. Synovial fluid was examined in five cases and in each had the characteristics of "Group I" fluid, as defined by Ropes and Bauer,[7] i. e., in each the total leukocyte count was less than 400 cells per cubic millimeter; the mucin clot, of good quality, and the relative viscosity, high. Synovial tissue was considered essentially normal in four cases and showed evidence of mild chronic inflammation in four cases.

CASE 3 (Fig. 5).—This 66-year-old housewife had experienced discomfort and slight swelling in both knees for a period of three years. Examination revealed moderate obesity, slight lateral instability of the left knee, and crepitus on motion of both knees. Synovial fluid contained no cellular elements, formed an excellent mucin clot, and had a high viscosity. The sensitized sheep-cell agglutination test (Ziff) was negative. Examination of synovial tissue disclosed slight hyperplasia of synovial cells and scattered infiltration of subsynovial tissue with inflammatory cells, especially in perivascular areas.

Gout

In our opinion the only pathognomonic change encountered in this material was the presence of urate deposits in eight of 23 cases of gout (35%). Only six of these 23 persons had demonstrable tophi elsewhere. The trauma of the biopsy was well tolerated in each case; instillation of hydrocortisone was occasionally helpful at the conclusion of the procedure. Since urates may be dissolved in formalin, absolute alcohol has been employed for fixation when the diagnosis of gout was suspected.

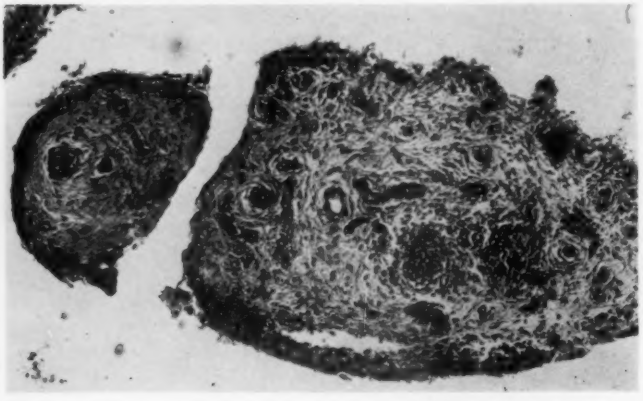

Fig. 5 (Case 3).—A 66-year-old housewife with osteoarthritis of both knees. In this section through a small synovial villus there is a mild perivascular inflammatory-cell infiltration. Hematoxylin and eosin; reduced 10% from mag. ×140.

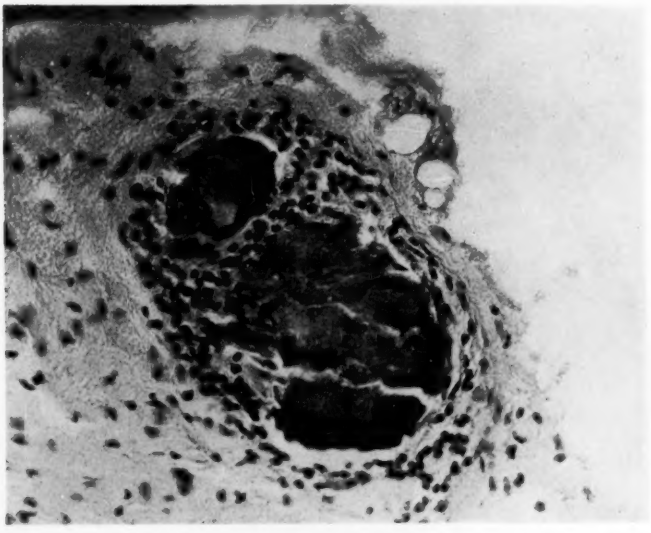

Fig. 6 (Case 4).—An area of urate deposition just beneath the synovial surface. Specimen obtained during an initial polycyclic attack of gout. Hematoxylin and eosin; reduced 10% from mag. × 400.

Case 4 (Fig. 6).—Two weeks before admission this 80-year-old man had experienced his initial attack of polyarthritis, which began in an elbow, migrating then to the left knee and right wrist. The knee was warm and tender and contained a moderate effusion. No tophi were visible. The serum urate was normal on three determinations. The synovial fluid nucleated-cell count was 6450 per cubic millimeter, of which 65% were polymorphonuclear leukocytes; mucin clot formation was poor and viscosity very low. In this synovial specimen there are multiple collections of urates surrounded by a narrow zone of lymphocytes and plasma cells; this specimen was fixed in formalin.

Case 5 (Fig. 7).—This 28-year-old man had experienced intermittent episodes of polyarthritis since the age of 20. Examination revealed evidence of synovitis involving the left ankle, the right knee, the proximal interphalangeal joints of both third fingers, the metacarpophalangeal joint of the right third finger, and both wrists. No tophi were observed. The serum urate level was 14 mg. %. The synovial tissue contained large areas of necrosis in which thin needle-like crystals

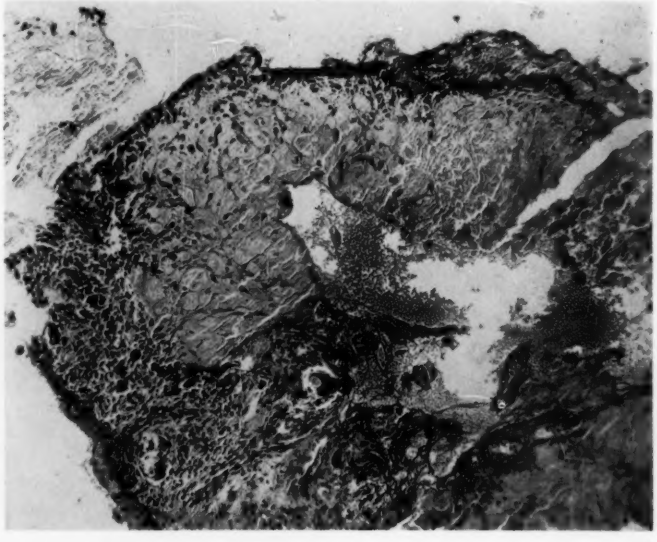

Fig. 7 (Case 5).—There is massive deposition of amorphous-appearing urates in the subsynovium, with a surrounding foreign-body giant-cell reaction. Hematoxylin and eosin; reduced 10% from mag. × 125.

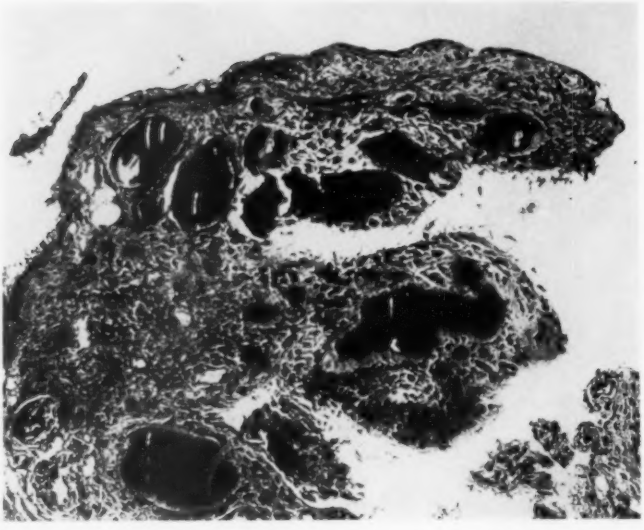

Fig. 8 (Case 5).—The large areas of urate deposit appear intensely black. Methenamine silver stain; reduced 10% from mag. × 150.

were present; about these areas was a foreign-body giant-cell reaction. The use of special staining procedures, such as the methenamine silver stain, may facilitate recognition of urates (Fig. 8).

Specific Infectious Arthritis

Synovial biopsy was performed on nine occasions where the diagnosis of specific infectious arthritis was eventually established. In the five cases with pyogenic infection there was elevation of the synovial fluid polymorphonuclear-cell count to the range of 100,000 to 400,000 cells per cubic millimeter. There has commonly been a purulent exudate on the synovial surface; on several occasions synovium from patients with definite rheumatoid arthritis and negative synovial fluid cultures showed a similar surface exudate. Helpful distinguishing features were the presence of considerable necrosis in cases of infection and the fact that the inflammatory-cell infiltrate is pre-

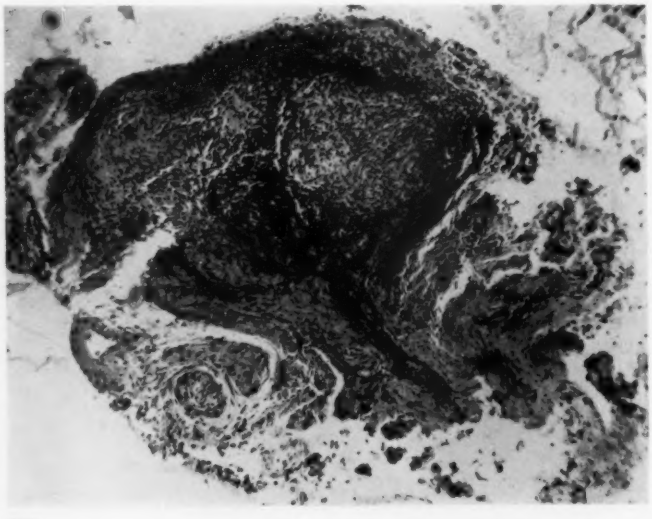

Fig. 9 (Case 6).—A 57-year-old businessman with monarticular involvement of the left knee. In this section of synovial tissue is an avascular epitheloid tubercle; the diagnosis of tuberculosis was subsequently confirmed by cultures positive for M. tuberculosis. Hematoxylin and eosin; reduced 10% from mag. × 100.

dominantly polymorphonuclear, in contrast to the mononuclear-cell infiltration in rheumatoid arthritis.

In one case of sporotrichosis involving bone and articulations and associated with positive cultures for Sporotrichum schenckii the causative organism was demonstrated in periodic acid-Schiff-stained sections.

Biopsy revealed characteristic epithelioid tubercles in one of three patients in whom the diagnosis of tuberculous arthritis was established by bacteriologic methods.

CASE 6 (Fig. 9).—This 57-year-old businessman had experienced pain and swelling in the left knee for a period of eight months. On examination the knee was warm and slightly reddened, with moderate capsular thickening and effusion. Examination of the synovium revealed avascular epithelioid tubercles compatible with the diagnosis of tuberculous synovitis. Synovial fluid culture later produced typical colonies of Mycobacterium tuberculosis.

Neurotrophic Joint Disease

Synovial tissue has been obtained from the knees of eight patients with neurotrophic arthropathy; seven of these patients had neurosyphilis. The distinguishing feature in five of these cases was the widespread deposition of lime salts in the subsynovium. This finding is not pathognomonic, however, since it has been observed in other conditions, especially where repeated trauma has occurred.

CASE 7 (Fig. 10.)—This 65-year-old woman had experienced pain and swelling in both knees, with instability of the right knee for two years. A diagnosis of tabes dorsalis had been made in 1930, and for two years thereafter she received injections of arsenic and bismuth. On physical examination the pupils reacted in accommodation but not to light. Position and vibratory sense were absent in the feet, and deep-pain sensation was greatly diminished. The right knee was enlarged, contained an excess of fluid, and was hypermobile in all directions. The synovial fluid nucleated-cell count was only 100 per cubic millimeter; the erythrocyte count was 28,000 per cubic millimeter, and the mucin clot formation good. Throughout the synovial tissue were numerous foci of lime salt deposition consistent with neurotrophic joint disease.

Summary

The material described in this study would not have been obtained had the Polley-Bickel synovial biopsy instrument not been available. Most of these patients would have refused conventional arthrotomy because of the expense and period of incapacity. Synovial punch biopsy, in contrast, is rapid, inexpensive, and sufficiently safe for routine use. When the procedure yields

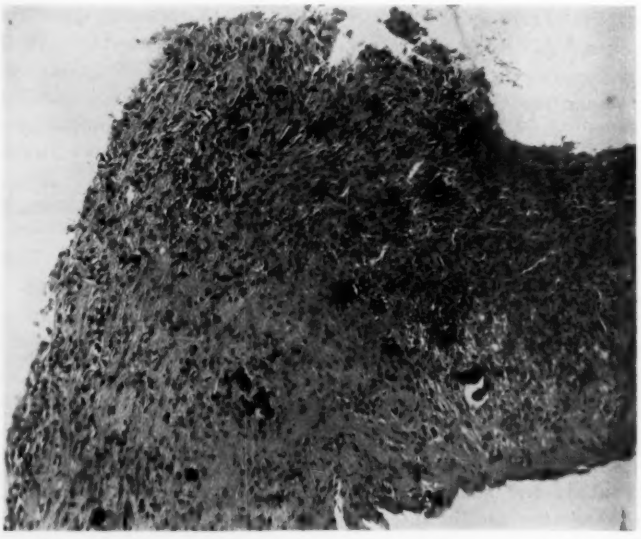

Fig. 10 (Case 7).—A 65-year-old woman with tabes dorsalis and neurotrophic joint disease of both knees. Throughout the synovial tissue are numerous foci of lime salt deposition consistent with neurotrophic arthropathy. Hematoxylin and eosin; reduced 10% from mag. × 150.

negative information or inadequate specimens of tissue it may be repeated or supplemented with arthrotomy.

An important limitation of punch biopsy is the fact that it is a blind procedure. Consequently, the gross findings that direct inspection might yield are not available and the selection of biopsy sites is a matter of chance. This latter factor is especially important in view of a study by Cruickshank [8] in which he demonstrated wide variations in appearance of the synovium from one area of the joint to another in rheumatic diseases.

In this study synovial biopsy was considered to be of diagnostic assistance in a worthwhile proportion of cases. Synovial changes present in the majority of cases of rheumatoid arthritis included (1) hyperplasia of the synovial intimal cells, often with increased villous formation of the synovial membrane; (2) subintimal inflammatory-cell infiltration with lymphocytes and plasma cells, often with follicle-like collections of these cells, and (3) increased vascularity, congestion, and edema. This combination of findings, in the absence of specific features pointing to some other diagnosis, is considered highly suggestive of rheumatoid arthritis, although, unfortunately, not diagnostic. Similar and indistinguishable changes were observed in most of the rheumatic diseases considered to be possible variants of rheumatoid arthritis, including juvenile rheumatoid arthritis, peripheral joint involvement in rheumatoid spondylitis, Reiter's syndrome, and apparent rheumatoid arthritis associated with psoriasis, positive L. E.-cell preparations, or Sjögren's syndrome. Biopsy was usually of help in differentiating rheumatoid arthritis from specific infectious arthritis, osteoarthritis, and gout. The other "connective tissue diseases" commonly showed similar and often milder and nonspecific synovial alterations.

In osteoarthritis synovial intimal-cell hyperplasia and subintimal inflammatory response were usually absent or slight. This finding, together with a more nearly normal nucleated-cell count, better mucin clot formation, and higher viscosity on examination of the synovial fluid, served to differentiate clearly osteoarthritis from rheumatoid arthritis.

It was very gratifying to find urate deposits in the synovium in about one-third of the patients with gout, since this established a definite diagnosis. Although urate deposits were demonstrated in one instance in the course of an initial episode of gout, it is not felt that this observation necessarily is of pathogenetic significance.

Early recognition of specific infectious arthritis is of extreme importance because of the danger of early irreversible damage and the fact that it represents one of the few potentially curable joint diseases. Whenever infection is suspected, synovial fluid and/or synovial tissue should be cultured for the common pyogens, tubercle bacilli, and fungi.

The finding of widespread lime salt deposits was characteristic of most of the cases with neurotrophic joint disease.

Periodic review of biopsy material with our students and staff has proved to be a valuable teaching exercise. In addition, the procedure has provided a ready source of synovial tissue for such studies as electron microscopy and tissue culture. At present the diagnostic value of the procedure is restricted more by difficulties in interpreting histologic changes than by inability to obtain satisfactory tissue specimens.

University of Michigan, University Hospital, Rackham Arthritis Research Unit.

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Recent Advances in the Knowledge of the Causes of Edema and in Diuretic Therapy

The Regulation of Water Balance and Plasma Sodium Concentration

ROBERT W. BERLINER, M.D., Bethesda, Md.

Considerable difficulties have been encountered in interpreting changes in the plasma sodium concentration. These difficulties derive from the unique place of sodium among the solutes of plasma. Ordinarily we are fully justified in considering deviations from normal of the concentration of a particular substance in plasma as indicating some disturbance in the metabolism of *that* substance. If the plasma glucose is high, we are safe in assuming that the rate of entry of glucose into the blood is high or its removal low. If the plasma potassium is high, we may conclude that there is an excess of potassium in the body or a disturbance in the distribution of potassium. But if we consider an abnormality of the plasma sodium concentration to indicate an abnormality of sodium metabolism, we will probably be wrong as often as we will be right. The unique place of sodium among the solutes of plasma lies in its abundance. Sodium, along with the anions which balance it, constitutes some 90% of the total solute of plasma. Since osmotic pressure is closely related to total solute concentration, the plasma sodium concentration reflects the osmotic pressure of the extracellular fluid. Furthermore, since we have reason to believe that the osmotic pressure of extracellular fluid is identical with that of intracellular fluid, we may generalize further to say that the concentration of sodium in the plasma generally closely reflects the effective osmotic pressure of all the body fluids. Since it is well known that the osmotic pressure of the body fluids is regulated by the intake and output of water, it follows that the plasma sodium concentration reflects not the state of sodium metabolism but the state of water balance. When a low plasma sodium is encountered we may conclude that there is some abnormality of the excretion of water. In some instances the abnormality of water excretion may be precipitated by losses of sodium, but it may also be due to a number of other circumstances which are quite unrelated to sodium loss or even sodium metabolism at all.

To reiterate, then, the plasma sodium concentration, with one minor exception, reflects the effective * osmotic pressure of the body fluids. Thus the concentration of sodium, paralleling osmotic pressure, is regulated by the appropriate adjustment of the intake and output of water.

We will not consider water intake, the physiology of which is largely apparent, but will review briefly the mechanism by which the output of water is regulated and effected. Since the kidney is the only organ in which the proportion of water to solute lost from the body can be regulated over a wide range

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* With respect to cell membranes.

and with some precision, we may consider this to be the effector organ, taking cognizance, of course, of the volume and composition of fluids lost from the body by routes other than in the urine.

We may then consider briefly how water and solute are reabsorbed as fluid passes from the glomerulus through the renal tubules. The reabsorption of water must be divided into three phases: In the first two phases reabsorption of water is directly dependent on the reabsorption of solute; in the third, the reabsorption of water is presumed to be independent. The order in which these three phases occur is well established; the identification of the anatomical sites, while not so definite, is probably adequately divided among (1) the proximal tubule, (2) the remainder of the nephron, but the distal convoluted tubule in particular, and (3) the collecting tubule and duct. The proximal tubule is freely permeable to water, and, consequently, as solute is reabsorbed in this segment water diffuses out so that the osmotic pressure of the fluid remains essentially identical to that of the surrounding extracellular fluid. The process which goes on in this segment, therefore, does not contribute to either the concentration or dilution of the urine, and the water reabsorbed is lost from the osmoregulatory process. Although the exact fraction of the filtered fluid which is thus lost to possible dilution is uncertain and probably variable, it is generally agreed that it is a major fraction of the glomerular filtrate.

The permeability to water of the distal tubule is quite different from that of the proximal segment. In the absence of pituitary antidiuretic hormone, the distal segment is relatively impermeable to water, and so as solute is reabsorbed in this segment, water *does not* follow along proportionately but remains behind, and the urine becomes diluted. Since, under most conditions, the bulk of the solute reaching the distal tubule is made up of sodium salts, it is specifically by the reabsorption of sodium, chloride, and bicarbonate in the distal tubule that the urine is diluted. We may thus see that the excretion of a dilute urine and the rapid removal of excess water from the body depends upon three factors related to the distal tubule: (1) An adequate amount of sodium-containing fluid must be delivered to this segment; (2) the segment must retain its capacity to remove these sodium salts from the urine, and (3) the tubule must have a low permeability to water. It is normally through the regulation of this permeability to water that the excretion of excesses of water is promoted or suppressed, for the action of the antidiuretic hormone of the posterior pituitary is upon the permeability of this segment to water. In the absence of antidiuretic hormone, the tubule approaches impermeability to water; in the presence of maximally effective amounts, the permeability to water increases to the point where the tubule wall presents virtually no barrier to the movement of water. Urine then leaves the distal tubule, isotonic as when it left the proximal segment, and a dilute urine can not be excreted.

It may seem strange to have described the action of antidiuretic hormone on the kidney without even mentioning the mechanism for elaborating a concentrated urine, when it is well known that the administration of antidiuretic hormone (ADH) leads to the formation of a maximally concentrated urine. While it would be wrong to imply that ADH has nothing to do with the formation of a concentrated urine, it is important to recognize that the most important action of ADH, from the standpoint of over-all water economy, is to prevent the excretion of a dilute urine and only secondarily to promote the excretion of a concentrated urine.

The mechanism for raising the concentration of the urine above that of the blood is too complex for consideration in this brief space. Suffice it to say (1) that it is not entirely dependent on antidiuretic hormone, since hypertonic urine *can* be formed when there is no circulating ADH and (2) that the activity of the mechanism is unmasked in the presence of ADH by the delivery to it of an isotonic rather than a hypotonic

fluid and by an increase of the permeability of the tubule in the region of the concentrating process.

The physiologic regulation of water excretion is under the control of the posterior pituitary hypothalamic system through the secretion of antidiuretic hormone, which in turn exerts its effect by modifying the permeability of the distal tubule to water. The release of antidiuretic hormone is normally determined by the effective osmotic pressure of the body fluids. Dilution of the body fluids, which tends to produce swelling of body cells, inhibits the release of antidiuretic hormone. With the disappearance of antidiuretic hormone, the permeability to water of the distal part of the nephron decreases; a dilute urine is produced, and the excess of body water is rapidly excreted in the urine. A rise in the effective osmotic pressure of body fluids leads to reversal of these events.

Normally, this mechanism operates with great precision and the plasma sodium and effective osmotic pressure of body fluids are maintained within remarkably narrow ranges. However, in stress and disease the mechanism is subject to a variety of disturbances, most of which are in the direction of preventing the rapid excretion of excesses of water and may lead, unless the administration of excess water is avoided, to dilution of the body fluids and hyponatremia.

The disorders of water excretion are, in general, of two types: first, and probably most commonly, inappropriate secretion of antidiuretic hormone—that is, secretion related to some stimulus other than an increase in the effective osmotic pressure of body fluids, and second, failure of delivery of adequate amounts of sodium salts to the diluting segment of the nephron.

Time will not permit consideration of the role of these factors in specific situations in which hyponatremia is commonly encountered. We may, however, mention a few of the stimuli which are known to cause the release of antidiuretic hormone—including pain, nausea, apprehension, and a number of drugs. It is well established that excessive release of antidiuretic hormone is produced by trauma of almost any sort and that prolonged antidiuresis is a usual accompaniment of surgery. Of course, the occurrence of antidiuresis is not a sufficient cause of hyponatremia but must be accompanied by an intake of water in excess of that required to maintain a normal osmotic pressure. Unfortunately such an inappropriately high intake of water is all too common, first, because water intake is frequently more a matter of habit than necessity, and second, because doctors and nurses have acquired the habit of forcing fluids and administering parenterally larger amounts of fluid than are necessary, depending on intrinsic regulatory mechanisms to get rid of the excess. This is safe when the regulatory mechanisms are working properly but may lead to trouble when they are not.

In conclusion, we may consider briefly the hyponatremia which may occur in those conditions in which diuretics are commonly used. We must distinguish between the situation in which the patient is both edematous and hyponatremic and that in which the patient has responded well, lost his edema, and become hyponatremic. In the latter case excessive diuresis may well have been indirectly responsible for the hyponatremia—the loss of extracellular fluid volume may lead to functional impairment of renal function so that inadequate volumes of fluid reach the diluting segment and at the same time there may be "inappropriate" secretion of ADH. This situation should be handled by interrupting the administration of diuretics and possibly by liberalizing salt intake so that extracellular fluid volume can be returned to a more normal level.

On the other hand, the cardiac who is both hyponatremic and edematous is not suffering from lack of salt. He, in fact, is usually one of the more seriously decompensated patients and only poorly responsive to diuretics. We have actually observed that occasionally such persons will lose their ex-

cesses of water and return their plasma sodium concentrations to normal at the same time that they lose large amounts of sodium in their urine when, in response to vigorous diuretic therapy, they finally obtain a good diuresis. Actually, short of this type of event the hyponatremia of such patients is most difficult to reverse. Hypertonic salt solutions should *not* be given. Rigid restriction of water intake, depending on obligatory and insensible losses to return osmotic pressure gradually to normal, is probably the safest and most satisfactory procedure. More attention, however, should be paid to the old and discarded practice of preventing such dilution by the restriction of water intake in severely decompensated cardiacs (and cirrhotics) who are subjected to rigid salt restriction.

National Institute of Health, Clinical Center (14).

Current Status of Aldosterone in the Etiology of Edema

AMOS H. LIEBERMAN, M.D., San Francisco

Shifts of fluid from the intravascular to the extravascular compartment are facilitated by appropriate changes in venous pressure, colloidal osmotic pressure, capillary permeability, and "tissue pressure." Development and subsidence of generalized edema cannot easily be explained on the basis of these factors alone. Starling [1] invoked diminished excretion by the kidneys to explain the "hydremic plethora" found in chronic congestive heart failure. Schroeder found that the capacity to excrete sodium chloride was greatly reduced in the edematous patient.[2] Restriction of salt intake to a level below urine output arrested edema accumulation or caused diuresis. Warren and Stead [3] administered sodium chloride to edema-forming patients and noted extracellular fluid accumulated before any increase in venous pressure was detected. They concluded that the edema of congestive failure resulted from failure of the kidneys to excrete salt and, secondarily, water for reasons then unkonwn.

Acute reduction in glomerular filtration rate in the experimental animal and man is followed by a significant decrease in renal sodium excretion. When decreased filtration rates were found in severely edematous patients with congestive failure, the concept of glomerular-tubular imbalance was suggested. A reduced quantity of sodium is delivered to the tubules, and, assuming normal reabsorptive activity, almost complete reabsorption of sodium results.[4] Decrease in glomerular filtration rate could also account for the edema seen in cirrhosis with ascites and in the nephrotic syndrome.[5] However, diminished filtration rates are not found in all subjects actively forming edema.[6,7] Spontaneous diuresis with relief of edema may occur without significant augmentation in glomerular filtration.[8] Methods presently available are inadequate to distinguish small changes in filtration rate. The possibility of such alterations, sufficient by themselves to explain the changed sodium excretion, cannot be excluded. However, edema does not occur in many cases of intrinsic renal disease in which glomerular filtration may be reduced to a level less than that found in most edema-forming patients. The predominance of renal tubular absorption is well illustrated in the heart failure of dogs produced by lesions of the pulmonic and tricuspid valves.[9] Impaired excretion of a sodium load is evident, although the glomerular filtration rate is unchanged from the control state. With clinical deterioration and onset of anorexia and cachexia, filtration diminishes.

Adrenocortical hormones promote sodium retention by increasing tubular reabsorption of filtered sodium. Overdosage with deoxycorticosterone in patients with Addison's disease may result in marked weight gain, frank edema, and the development of a clinical picture similar to that of congestive

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failure. Accordingly, a search was made for sodium-retaining activity in the urine of patients with diseases of the heart, liver, and kidneys during accumulation of edema. Biological assay revealed increased amounts of a potent sodium-retaining and potassium-excreting substance that proved similar to a compound isolated from the adrenal cortex and identified as aldosterone. Crystalline material obtained from urine of patients with congestive failure and the nephrotic syndrome proved to be identical to aldosterone.[10,11]

Increased amounts of aldosterone are found in the adrenal venous blood [12] and the urine [13] of dogs in whom congestive failure has been produced by pulmonary artery constriction. Adrenalectomy is followed by prompt diuresis and loss of edema. Administration of deoxycorticosterone results in reaccumulation of fluid.

Abnormal output of aldosterone is found only in those patients with heart disease who demonstrate generalized fluid retention. Normal amounts of aldosterone are found in the urine of patients who are not collecting fluid on a normal diet. Isolated left ventricular failure with congestion solely of the pulmonary circulation is not associated with increased aldosterone, which rises only when generalized edema appears. Large amounts of aldosterone may be seen with "right-sided" failure alone.[14] The highest levels are seen whenever active accumulation of fluid is present. Smaller increases or normal excretion of aldosterone may be seen during static edema. With improvement of myocardial function, diuresis may occur, in association with reduced levels of aldosterone. Significant changes in myocardial function without the interfering effect of alterations in salt and water balance were produced in a heart patient by Wolff.[15] Severe decompensation was produced by physical stress while the patient was maintained on a constant normal intake of sodium. Urinary sodium fell considerably, body weight increased, and aldosterone output rose. When complete recompensation was achieved in the same patient by bed rest and digitalization alone, urinary sodium rose, diuresis occurred, and aldosterone returned to normal.

These changes in aldosterone output are reflected by appropriate shifts in sodium and potassium balance. During rapid edema formation, sodium may virtually disappear from the urine. With improvement in the underlying disease, sodium content of urine rises and diuresis is noted. During diuresis, potassium is retained [16] and suggests a negative potassium balance had existed during fluid accumulation. In the patient with large amounts of edema, total body sodium is increased and total body potassium decreased when measured by isotopic sodium and potassium.[17]

The finding of normal or elevated glomerular filtration rates in some patients with the nephrotic syndrome suggests that enhanced tubular reabsorption of sodium exists. Production of a nephrotic syndrome experimentally in rats is associated with an increased level of aldosterone in adrenal venous blood.[18] Greatly increased amounts of aldosterone are found in the urine of patients who are collecting edema.[19] Since these patients usually have very low concentrations of serum albumin, reduction in colloidal osmotic pressure of plasma undoubtedly contributes to edema formation. Nevertheless, the repeated administration of intravenous human serum albumin may increase the concentration of serum albumin, raise the oncotic pressure of plasma, and be ineffective in increasing sodium output.[20] A successful diuresis is achieved only in those cases in whom aldosterone excretion has decreased. Similarly, the loss of sodium seen after administration of corticosteroids to these patients is accompanied by reduction in aldosterone output.

Higher levels of aldosterone are found in the urine of patients with ascites due to cirrhosis of the liver than in patients with comparable edema due to other causes. Impaired inactivation of the hormone by the liver may result in a larger proportion appearing in the urine in a biologically active

form. Preliminary data on administering equal amounts of aldosterone to normal subjects and patients with decompensated liver cirrhosis suggest that a higher per cent of the administered hormone may be recovered from the urine of the latter group.[15] The highest aldosterone activity and strongest sodium retention can be found during accumulation of ascites. The prompt and striking increase in aldosterone activity seen in these cases cannot be explained on the basis of impaired steroid inactivation alone. When fluid collection is less brisk, aldosterone output is not as striking. In this condition, too, the serum protein concentration only contributes to the collection of edema, since spontaneous diuresis may occur despite continued hypoalbuminemia.[21] Modest elevations in aldosterone excretion may be seen in patients with acute hepatitis.[22] High aldosterone activity may be accompanied by normal sodium output, suggesting that an increased production of steroid is not present but rather conjugation of the free hormone by the liver is decreased. With convalescence, aldosterone output decreases within normal limits.

The adrenal gland appears to be necessary for the fluid retention seen in these patients. When total adrenalectomy has been performed in an occasional instance of intractable ascites, loss of edema has promptly ensued.[23,24] Adrenalectomy likewise promotes loss of excess fluid in the dog where constriction of the thoracic portion of the inferior vena cava has resulted in gross ascites.[13] When deoxycorticosterone is administered to these animals, ascites reaccumulates. More recently, Amphenone B (1,2-bis-[*p*-aminophenyl]-2-methyl-1-propanone dihydrochloride), an agent believed to inhibit adrenocorticoid synthesis and especially aldosterone, has been administered to a few patients with ascites. In some instances, diuresis, sodium loss, and decrease of ascites ensued while aldosterone output decreased.[25]

Thus, an inverse relationship between sodium and aldosterone excretion is evident in all edematous patients, regardless of the etiology. Inability to excrete sodium loads is evident at a time when the glomerular filtration rate may be elevated, normal, or depressed. The level of aldosterone is intimately related to the status of the underlying disease. Measures aimed at improving function of the diseased heart, liver, and kidneys are most successful in initiating diuresis, excretion of excess sodium, and reduction of aldosterone levels toward normal. In congestive heart failure, the competent use of digitalis, bed rest, and correction of such complications as infection, anemia, and thyrotoxicosis will relieve edema most satisfactorily. Similar results may be obtained with the use of appropriate diet and bed rest in cirrhosis of the liver and with corticosteroid therapy in patients with the nephrotic syndrome. Therapy directed toward correcting the physiological defects in, but not ameliorating, the underlying disease is less successful in initiating a diuresis. The use of serum albumin in patients with liver disease and the nephrotic syndrome may correct the severe hypoproteinemia but fail to achieve more than a very transient and slight diuresis of water and sodium. Measures aimed solely at relief of edema are usually associated with further increase in aldosterone output. Sustained diuresis is unlikely to result after the use of diuretic drugs, while edema promptly accumulates once these agents are discontinued. In an occasional patient with congestive heart failure, however, the excess fluid present may directly impair function of the heart or depress some aspect of renal function. In such a person, the use of diuretic agents or cation-exchange resins may be associated with reduction in aldosterone excretion.[26]

When deoxycorticosterone is administered to normal animals or man,[27,28] edema is not produced. Although sodium and water are retained initially, within a few weeks polyuria and polydipsia supervene and further sodium retention ceases. A similar clinical picture has been noted in man in the presence of adrenal tumor or hyperplasia

secreting excess amounts of aldosterone.[29] Recently, large doses of aldosterone were administered for several weeks to normal subjects and to patients with Addison's disease maintained on cortisone.[30] Initially, sodium and water were retained in both groups. After a period varying from several days to more than a week, sodium output rose despite continued administration of aldosterone. The increase in body weight did not exceed more than 2 to 3 kg. In contrast, when deoxycorticosterone is administered to adrenalectomized dogs, retention of sodium and fluid is seen as long as the steroid is continued. Accidental overdosage with deoxycorticosterone in patients with Addison's disease receiving no other medication may result in marked weight gain, frank edema, and even signs and symptoms of congestive heart failure.[31] Marked edema may also be induced in chronic alcoholics, possibly on an ill-defined nutritional basis, by administration of deoxycorticosterone and salt. In these subjects, blood proteins, liver function and histology, and heart and kidney functions may be entirely normal.[32]

It is clear from these observations that the edematous patient does not resemble the normal subject in his response to a sodium-retaining hormone. In these persons, as in the patient with Addison's disease, the sodium retention following administration of adrenal hormones is greater than seen with comparable doses in normal subjects. When adrenalectomy has been attempted in the therapy of intractable ascites associated with cirrhosis of the liver, maintenance with only 18.5 to 25.0 mg. per day of hydrocortisone was associated with reaccumulation of ascites.[23] Dosages of this magnitude are not ordinarily associated with sodium retention in a normal person.

When a sodium load is administered for several days to a normal person, urinary sodium promptly rises and after two to three days approaches intake level, while aldosterone output falls to insignificant levels. Suppression of aldosterone in edematous patients by salt loading has been demonstrated, but more sodium chloride must be given, more fluid is retained, and more weight is gained than in normal subjects, while aldosterone output usually does not fall to normal levels.[33] When a patient with idiopathic edema (Fig. 1) received 32 gm. of sodium chloride over a three-day period, no increase in urinary sodium nor decrease in urinary aldosterone was evident after retention of a quantity of sodium sufficient to suppress completely aldosterone in normal subjects.

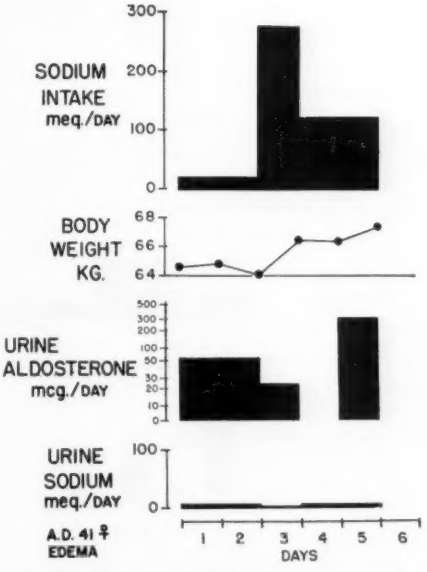

Fig. 1.—Effect of sodium loading in a patient with idiopathic edema. Despite administration of 32 gm. of sodium chloride on Days 3 to 5, sodium output in the urine did not rise, while aldosterone excretion was higher on the third day of sodium loading than in the control period.

Change from the recumbent to the erect position by normal subjects is followed by increased output of aldosterone.[34] The edematous subject appears more sensitive to similar alterations in position. A patient with idiopathic hypoproteinemia and edema, maintained on a moderately restricted sodium intake, was found to be in negative sodium balance while at bed rest (Fig. 2). Ambulation was followed by marked reduction in sodium output, and elevated aldoster-

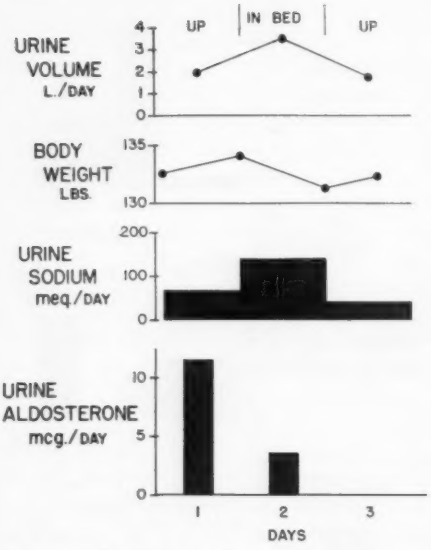

Fig. 2.—Effect of position on aldosterone excretion in a patient with idiopathic hypoproteinemia and edema. Note the decrease in aldosterone output associated with increased output of sodium and water when patient was put to bed.

one was noted. When the patient was put back to bed, the urinary sodium increased while aldosterone output fell to within normal limits. Similar changes in aldosterone output may explain the frequent spontaneous improvement and diuresis seen in edematous patients admitted to the hospital and put to bed.

These clinical observations strongly suggest aldosterone has a role in the causation and maintenance of edema seen in disease states. It is still not clear why increased secretion of this hormone should be evoked in diseases of the heart, liver, and kidneys.

Since aldosterone acts to promote sodium retention and potassium excretion, it is not surprising that appropriate alterations in intake of these substances influence aldosterone output. Deprivation of sodium or potassium loading results in augmented aldosterone secretion, while sodium loading or potassium depletion may be followed by virtual disappearance of aldosterone from urine.[35] Although these changes in aldosterone output may well be a consequence of the associated changes in extracellular fluid volume, there is evidence to suggest that potassium exerts a more direct effect upon aldosterone.[36] Contraction of extracellular fluid volume is a strong stimulus to aldosterone secretion, but expansion of extracellular fluid inhibits aldosterone. Maintenance of constancy of extracellular fluid results from the effects of aldosterone on sodium output, since changes in water excretion follow in an attempt to preserve constant osmolarity of body fluids. The intravascular volume has been suggested as the component of extracellular fluid most concerned with aldosterone regulation. Phlebotomy may be associated with increased levels of aldosterone, which subside when the red cells are reinfused.[37] However, although expansion of plasma volume in normal persons does succeed in reducing the elevated aldosterone output consequent to sodium deprivation, continued administration of salt-poor albumin for a nine-day period does not reduce aldosterone output below the normal range.[37] In patients with chronic congestive failure, the association of increased blood volume with high aldosterone output casts doubt on the idea that the total intravascular volume regulates aldosterone secretion. The crucial component may be circulation to a specific area, the site of a volume receptor which transmits impulses regulating aldosterone. The location or mechanism of such a receptor is unknown. Recently, the diencephalon has been implicated as the source of a humoral agent that is able to act directly upon the adrenal cortex and stimulate aldosterone.[38]

It is not known whether the increase in aldosterone seen in the cardiac patient initiates or is a consequence of transudation of fluid. In the patient with the nephrotic syndrome, however, it seems likely that the reduced concentration of serum proteins allows fluid to escape from the blood to the extravascular compartment. The consequent hypovolemia might provide the stimulus for excess aldosterone secretion in order to maintain the integrity of the circulation.

When ascites accumulates in the patient with cirrhosis of the liver after abdominal paracentesis, it is evident that there is a rapid shift of fluid from other sites into the peritoneal cavity. In the dog, constriction of the thoracic portion of the inferior vena cava results in accumulation of edema and elevated aldosterone levels. If these animals are maintained on a sodium-free diet, fluid still collects in the abdominal cavity, suggesting that aldosterone does not initiate the fluid retention seen.[39]

It is possible that abnormal sequestration of retained fluid in the abdominal cavity results in continued secretion of aldosterone in patients with cirrhosis of the liver. In other edematous patients, the excess of extracellular fluid may fail to correct the defect of fluid distribution or hemodynamics which stimulates aldosterone secretion. Correction of this defect may occur after accumulation of very large amounts of extracellular fluid. In such persons, edema would be static and aldosterone levels normal or only slightly increased (Fig. 3).

At present, we can only speculate on the reasons for the increased aldosterone levels seen in patients with edema. It is evident, however, that the problem of edema cannot be properly considered without reference

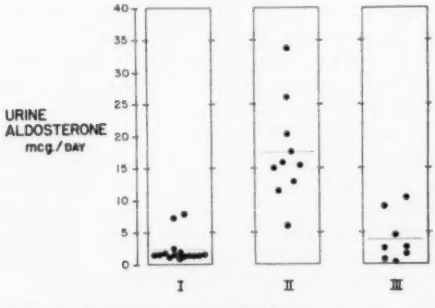

Fig. 3.—Aldosterone output in normal subjects and in patients with edema. Group I: normal subjects. Group II: edematous subjects with congestive cardiac failure, nephrotic syndrome, and cirrhosis of the liver. These patients were actively retaining fluid. The illustrated values in this group represent minimal estimates of the actual aldosterone excretion. Group III: edematous patients with congestive cardiac failure or cirrhosis of the liver. During the period of observation, edema was static and body weight did not change significantly.

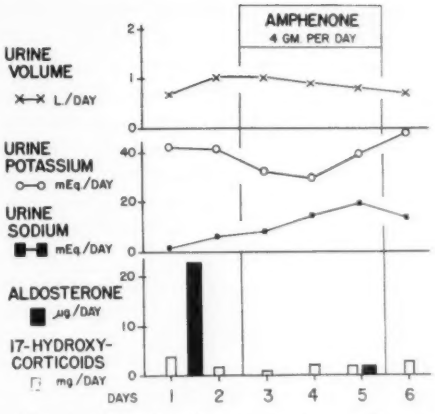

Fig. 4.—Administration of Amphenone B to a patient with the nephrotic syndrome. Despite the marked fall in aldosterone excretion, sodium output rose only slightly.

to the physiological principles that govern aldosterone secretion in the normal subject.

It would be an oversimplification to imply aldosterone is the sole cause of sodium retention in all circumstances. Variations in excretion of sodium occur in patients with Addison's disease maintained on a constant dose of adrenocortical hormone.[40] Abnormalities of renal function and hemodynamics must play a part, especially in advanced cases of edema. When Amphenone B (Fig. 4) was administered to a patient with the nephrotic syndrome, aldosterone output decreased to normal levels but no striking increase in sodium output was noted. The serum creatinine concentration before treatment was 1.4 mg. %; the endogenous creatinine clearance, 50 ml. per minute. The serum creatinine concentration rose after administration of Amphenone to 3.0 mg. %, suggesting that the glomerular filtration rate had decreased sufficiently to prevent further excretion of sodium by the kidney.

Impaired excretion of water loads is a prominent feature in many patients with edema. This disturbance in water balance is especially evident in those persons with hyponatremia and increased total body sodium. Secretion of antidiuretic hormone must persist inappropriately in these pa-

tients, since the osmolarity of the body fluids is lowered.

The physiological disturbances in edematous patients are complex and undoubtedly involve alteration in several mechanisms ordinarily concerned with sodium retention and maintenance of volume of body fluids. Although excess aldosterone secretion contributes to fluid accumulation, further studies are needed to define the exact role of aldosterone and these other mechanisms of sodium retention in the etiology of the edema in these patients.

Summary

Enhanced tubular reabsorption appears to be primarily responsible for the sodium retention found in edematous patients with diseases of the heart, liver, and kidneys. In the patients, as well as in normal subjects, there is a close inverse relation between sodium and aldosterone excretion. In the absence of the adrenal glands, sodium conservation cannot occur, nor can edema be maintained. However, administration of exogenous aldosterone to normal subjects in chronic experiments does not result in continued sodium and fluid retention. It is evident some other factor or factors, in addition to excess aldosterone secretion, must contribute to the edema formation found in patients. Further study is needed to clarify the precise role of aldosterone and these other factors in the pathogenesis of edema.

Stanford University School of Medicine, Department of Medicine (15).

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Aldosterone Antagonists

GRANT W. LIDDLE, M.D., Nashville, Tenn.

For 30 years it has been known that steroidal hormones of the adrenal cortex tend to promote sodium conservation by the kidneys. It is now believed that the most potent sodium-retaining hormone of the adrenal cortex is aldosterone.

It has been shown repeatedly that the ability of normal persons to conserve sodium in the face of sodium deprivation is dependent upon the secretion of relatively large quantities of aldosterone by the adrenals.[1,2] Lack of ability to secrete aldosterone in the face of sodium deprivation explains the serious renal sodium wasting which is characteristic of patients with untreated Addison's disease. It has also been shown that the common disorders of the circulation which are accompanied by maximal tubular reabsorption of sodium and edema formation (e. g., cirrhosis, nephrosis, and congestive heart failure) are associated with increased secretion of aldosterone.

For the sake of perspective it should be emphasized that aldosterone does not *cause* edema. But the presence of aldosterone or some similar agent is one of the necessary conditions for edema formation in the ordinary case of cirrhosis, nephrosis, or congestive heart failure. The circulatory disturbance which provokes aldosterone secretion is also usually one which impairs to some extent renal hemodynamic function in such a way as to produce a glomerulotubular imbalance in favor of sodium retention. As a general rule, edema occurs only in the presence of sodium-retaining steroids *and* some sort of circulatory insufficiency. The *presence* of edema implies an increase in total body sodium and means that there has been diminished renal excretion relative to intake of sodium. The *distribution* of the edema is determined by the type of circulatory disorder and not by the aldosterone-renal tubular mechanism for sodium conservation.

It is possible to break the chain of events leading to edema in a variety of ways. First, by correcting the primary disturbance which provokes the secretion of aldosterone (e. g., by giving intravenous albumin or by improving cardiac function) it is possible to bring about a decrease in aldosterone levels and thereby induce a diuresis. Second, by inhibiting the biogenesis of steroids within the adrenal cortex it is possible to bring about a decrease in aldosterone levels and thereby induce a diuresis. An agent capable of doing this is Amphenone B (1,2-bis-[*p*-aminophenyl]-2-methyl-1-propanone dihydrochloride).[3] Third, by blocking the action of aldosterone within the renal tubule it is possible to induce loss of sodium in the urine. This will be of central interest in the present paper. Fourth, by administering pharmacologic agents which interfere with the idiorenal mechanisms for sodium reabsorption it is possible to induce a diuresis. All of the effective diuretic agents now in general use fall into this category.

Aldosterone Antagonism: A New Mechanism of Diuresis

Recently steroid chemists have developed two new compounds [4] which block the action of aldosterone at the renal tubular level.

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From the Department of Medicine, Vanderbilt University School of Medicine.

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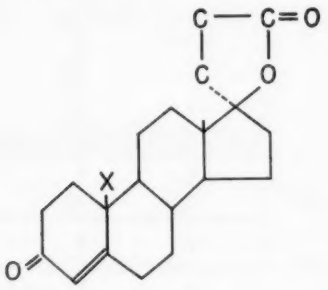

Fig. 1.—Chemical structure of spirolactone. In the compound designated by the code number SC-5233, *X* represents a methyl group. In SC-8109, *X* represents a hydrogen atom. This, then, is the "19-nor" analog of SC-5233. SC-8109 has been found to be several times more potent than SC-5233, both parenterally and orally. Each compound is several times more potent when injected intramuscularly as an oily suspension than when given orally.

These are the steroid-17-spirolactones, the structures of which are designated in Figure 1. In the present paper this *type* of compound will be referred to simply as "spirolactone."

On the basis of studies carried out by Kagawa et al.[5] and those performed in this laboratory,[6] there has evolved the concept that spirolactone is an aldosterone antagonist. Reasons for this are first, that the effects of spirolactone are opposite to those of aldosterone and second, that spirolactone is effective only in the presence of aldosterone or biologically similar steroids.

Effects of Spirolactone on Urinary Electrolytes

Before turning our attention to the renal effects of the aldosterone antagonist we might review the actions of aldosterone itself (Fig. 2). The administration of aldosterone results in an acute fall in Na^+ excretion. At the same time there is a fall in Cl^- excretion and a decrease in urinary volume. As Na^+ disappears from the urine certain alternative urinary cations (K^+, H^+, and NH_4^+) appear in increased quantities.

Frequently the physiological actions of steroids are most dramatically illustrated by observing the consequences of their abrupt withdrawal. Following the withdrawal of

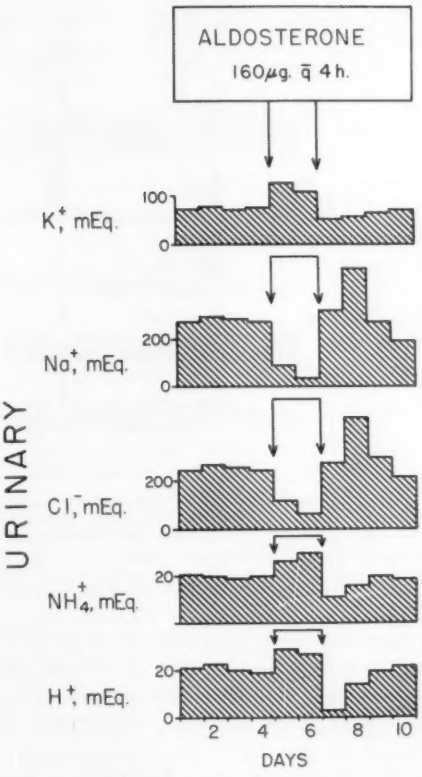

Fig. 2.—Effects of aldosterone upon urinary electrolytes in a normal man maintained on constant dietary intake. Synthetic aldosterone-21-monoacetate in 5% aqueous ethanol was injected intramuscularly in doses of 320μg. every four hours for two days. The racemic synthetic compound has only one-half the biologic activity of the naturally occurring *d*-isomer. Urinary electrolytes are represented in milliequivalents per 24 hours. In this and subsequent figures the symbol H^+ represents titratable acid of the urine, with use of pH 7.4 as the end-point.

aldosterone (Fig. 2, Days 7 and 8) there is an increase in urinary Na^+, Cl^-, and volume and a decrease in urinary K^+, H^+, and NH_4^+.

The administration of spirolactone simulates the abrupt withdrawal of aldosterone in all of its effects. There is an increase in urinary Na^+, Cl^-, and volume, accompanied usually by a slight decrease in urinary K^+, a very marked decrease in urinary H^+, and a moderate decrease in urinary NH_4^+ (Figs. 3, 4, 5, and 8).

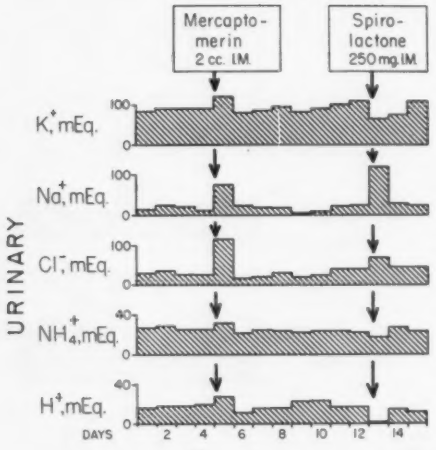

Figure 3

Fig. 3.—Comparative effects of mercaptomerin (Thiomerin) and spirolactone (SC-8109) upon urinary electrolytes in a normal 24-year-old man maintained on a constant diet containing 30 mEq. of Na^+ per day. Each treatment was given at the beginning of a "metabolic day" as a single intramuscular injection. Spirolactone, 250 mg., was suspended in 5 ml. of sesame oil.

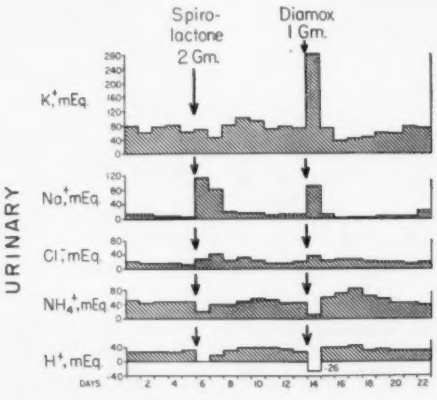

Figure 4

Fig. 4.—Comparative effects of spirolactone (SC-8109) and acetazolamide (Diamox) upon urinary electrolytes in a normal man maintained on a constant diet containing 22 mEq. of Na^+. Each agent was administered orally for one day in divided doses at eight-hour intervals.

Spirolactone differs from other diuretic agents in that it is capable of blocking *all* of the actions of aldosterone. Of particular importance is the action of spirolactone on potassium excretion. Spirolactone blocks the potassium-losing action of aldosterone, whereas all other diuretics tend to increase the excretion of potassium. Studies with two classes of diuretics, the mercurials and the carbonic anhydrase inhibitors, serve to illustrate the distinctive action of spirolactone.

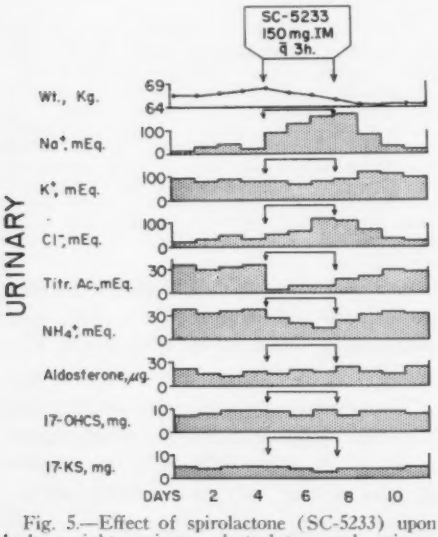

Fig. 5.—Effect of spirolactone (SC-5233) upon body weight, urinary electrolytes, and urinary steroids (aldosterone, 17-hydroxycorticoids, and 17-ketosteroids) in a 35-year-old patient with nephrosis. The spirolactone was suspended in sesame oil, 50 mg. per milliliter.

It has been suggested[7] that mercurial diuretics act primarily to block the renal tubular reabsorption of chloride.* Since Cl^- is a strong anion, it requires the concomitant excretion of such cations as Na^+, K^+, and NH_4^+. The effects of a mercurial diuretic, mercaptomerin, are contrasted with those of spirolactone in Figure 3. Although comparable degrees of Na^+ loss were induced by both agents, the mercurial diuretic caused a marked increase in Cl^- and K^+ excretion, with little change in H^+ and NH_4^+ excretion, whereas spirolactone caused a slight increase in Cl^- excretion and

* Berliner has recently pointed out that the observed effects of mercurial diuretics can be explained by postulating that their primary action is the inhibition of sodium reabsorption by the proximal tubule, with chloruresis occurring as a passive consequence thereof.[8]

a decrease in excretion of K^+, H^+, and NH_4^+.

The carbonic anhydrase inhibitors decrease the availability of H^+ to the cation-exchange mechanism by which Na^+ is reabsorbed from and H^+ is secreted into the tubular lumen. Lack of H^+ secretion appears to facilitate secretion of K^+ by the distal tubule, and so as an ultimate consequence of carbonic anhydrase inhibition there is an increase in K^+ excretion as well as Na^+ excretion.[9] The effects of a carbonic anhydrase inhibitor, acetazolamide, are contrasted with those of spirolactone in Figure 4. Although comparable degrees of Na^+ loss were induced by both agents, acetazolamide caused a marked increase in K^+ excretion, whereas spirolactone did not. Both compounds caused increases in excretion of Cl^- and decreases in urinary H^+ and NH_4^+.

Clinical Use of Spirolactone in Edematous Patients

Patients who, in the course of such diseases as cirrhosis, nephrosis, or congestive heart failure, reach the point where they are excreting only small quantities of sodium have generally been found to be secreting abnormally large quantities of aldosterone. These patients respond to spirolactone with an increase in urinary Na^+ and Cl^- and a decrease in urinary H^+, and NH_4^+. K^+ excretion usually falls slightly.

Although a massive one-day diuresis in patients treated with spirolactone has never been observed, continued treatment over several days can be completely satisfactory. Figure 5 depicts a study performed in a patient with nephrosis. This man maintained his edema despite a relatively low-sodium diet. Treatment with spirolactone for three days, however, led to a diuresis of 8 lb. of edema fluid, which was enough to make him comfortable.

Therapeutic Use of Spirolactone in Combination with Other Diuretics

Normal persons on a normal sodium intake exhibit a predominantly natriuretic response with only a minor kaliuretic response to conventional diuretics. Unfortunately, patients who are secreting large quantities of aldosterone often exhibit a predominantly kaliuretic rather than natriuretic response to the conventional diuretic agents. The use of an aldosterone antagonist in combination with conventional diuretics tends to restore the pattern of response to normal. As illustrated in Figure 6, spirolactone has been

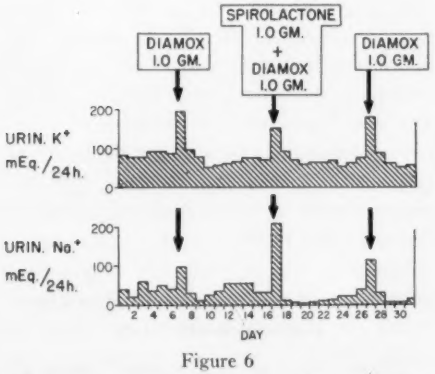

Figure 6

Fig. 6.—Effects of acetazolamide (Diamox), alone and in combination with spirolactone, upon urinary Na^+ and K^+ of a normal man maintained on a constant diet containing 30 mEq. of Na^+. On each occasion, acetazolamide was given orally in two doses (0.5 gm. at the beginning of the metabolic day and 0.5 gm. eight hours later). Spirolactone (SC-8109) was given orally in doses of

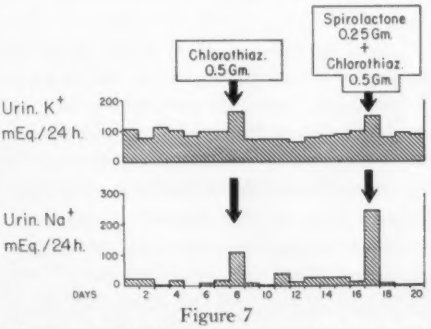

Figure 7

0.5 gm. at the beginning of the metabolic day and 0.5 gm. eight hours later.

Fig. 7.—Effects of chlorothiazide, alone and in combination with spirolactone, upon urinary Na^+ and K^+ of a normal man maintained on constant diet containing 22 mEq. of Na^+. Chlorothiazide was given orally in two doses (250 mg. at the beginning of the metabolic day and 250 mg. eight hours later). Spirolactone (SC-8109 in sesame oil, 50 mg. per milliliter) was given intramuscularly in a single dose at the beginning of the metabolic day.

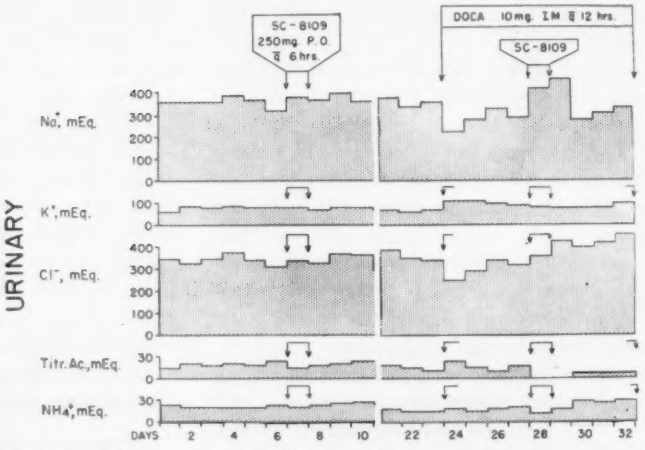

Fig. 8.—Left: lack of effect of spirolactone (SC-8109) administered orally in doses of 250 mg. every six hours for one day to a 30-year-old adrenalectomized woman with Addison's disease maintained on a constant diet containing 360 mEq. of Na^+. Right: effectiveness of spirolactone in oral doses of 250 mg. every six hours when superimposed upon treatment with desoxycorticosterone acetate (Doca) in oil. In order to avoid severe manifestations of adrenal insufficiency the patient received, in addition to high-salt intake, 1.25 mg. of methylprednisolone (6-methylprednisolone, Medrol) every eight hours throughout the entire study. In this dosage the electrolyte-regulating effect of methylprednisolone is negligible.

found to augment the natriuretic while diminishing the kaliuretic action of acetazolamide. Similar results have been observed in studies employing spirolactone in combination with chlorothiazide (Fig. 7).

A Further Note on the Mode of Action of Spirolactone

Spirolactone differs from the conventional natriuretic agents in that it exhibits its characteristic effects only in the presence of aldosterone-like steroids, whereas the conventional agents can act in either the presence or absence of aldosterone-like steroids. It has been shown previously by Kagawa et al.[5] that spirolactone has practically no effect on urinary sodium and potassium in the adrenalectomized rat maintained on high-sodium diet without steroid replacement. Similar observations were made on adrenalectomized dogs in this laboratory.[6] As illustrated in Figure 8, the administration of spirolactone had little or no effect on urinary electrolytes in patients with Addison's disease maintained on high-sodium intake without steroid therapy. However, when the same patients were maintained on a high-sodium diet plus deoxycorticosterone acetate (Doca) they then responded to spirolactone with the usual increases in urinary Na^+ and Cl^- and decreases in urinary H^+, NH_4^+, and K^+.

Urinary 17-ketosteroid, 17-hydroxycorticoid, and aldosterone levels are affected little by short (one- to three-day) courses of treatment with spirolactone (Fig. 5). "Either no change or a slight increase in aldosterone levels occurs during spirolactone-induced sodium diuresis. In short, all of the evidence favors the view that spirolactone blocks the action of other steroids at a peripheral site and does not block the secretion of steroids by the adrenal glands. It is to be expected that with more prolonged treatment the spirolactone-induced sodium loss would intensify the stimulus to aldosterone secretion. Probably the characteristic response to spirolactone therapy, then, will include that of increased levels of aldosterone in plasma and urine.

Effects of Spirolactone in Primary Hyperaldosteronism

Salassa, Mattox, and Power[10] have administered spirolactone to a patient having an aldosterone-secreting tumor, with very interesting results. Prior to treatment with spirolactone the patient had hypokalemic alkalosis and markedly elevated urinary

aldosterone values (32μg. and 56μg. per day). Treatment with spirolactone in doses of 1.0 to 1.9 gm. daily for 19 days resulted in a strongly negative sodium balance and a positive potassium balance, with partial correction of the hypokalemic alkalosis. Withdrawal of spirolactone permitted reversal of these effects. After removal of an adrenal cortical adenoma urinary aldosterone values fell to very low values (less than 0.1μg. per day). Treatment with spirolactone at this time had little effect on urinary sodium and potassium.

Spirolactone in Patients with Uremia

Two edematous patients in the present study failed to respond to ordinary doses of spirolactone. Both of these patients had congestive heart failure and chronic glomerulonephritis, with blood N. P. N. ranging from 60 to 120 mg. per 100 ml. and glomerular filtration rates ranging from 10 to 25 ml. per minute. Despite the presence of edema and the relatively low levels of urinary sodium (8 to 40 mEq. per day), neither of these patients had abnormally high urinary aldosterone levels. It is suggested that in advanced renal failure aldosterone may be relatively unimportant in the pathogenesis of edema. Under such circumstances one would not expect an aldosterone antagonist to be highly effective. For that matter, any natriuretic agent is likely to be limited in its effectiveness in patients with marked renal insufficiency.

Side-Effects of Spirolactone

In some 40 subjects who have received spirolactone 1 side-effect has been noted. Those receiving SC-8109 in oral doses exceeding 2 gm. per day have frequently experienced drowsiness and ataxia lasting several hours. Such large doses are rarely needed, however, to bring about the aforementioned effects on electrolyte excretion.

Comment

It is difficult to predict the ultimate role of spirolactone in medicine. From the standpoint of natriuretic potency the diuretic agents already available leave little to be desired. Many of the conventional agents have the disadvantage, however, of causing derangements of electrolyte balance. Potassium wasting is a particularly common complication of diuretic therapy, and spirolactone is unique in that it causes natriuresis without kaliuresis. Perhaps spirolactone will have some value in combination with other diuretics by augmenting the natriuretic while diminishing the kaliuretic effects of the latter. Possibly spirolactone will have some place as a diagnostic and investigative tool which can be used to demonstrate to what extent, in a given situation, sodium retention and potassium excretion are steroid-dependent. Perhaps it will have heuristic value in the hands of renal physiologists in their efforts to unravel the mechanisms of renal tubular function. Regardless of its ultimate utility, spirolactone is already of some historical importance in that it has made possible the unequivocal demonstration that there can be such a thing as a "salt-losing steroid" and that a steroid having little apparent activity of its own may nevertheless act as an antagonist to the actions of another.

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Nonmercurial Organic Diuretics

Their Action and Application

KARL H. BEYER Jr., M.D., Ph.D., West Point, Pa.

The renotropic effect of diuretic agents is employed clinically to induce a more favorable balance between the glomerular filtration of plasma water and the reabsorption of "salt" and water by the renal tubules. As illustrated in Figure 1, it is attractive to consider that with the pathogenesis of cardiovascular-renal disease there may be phases of progressive imbalance between the reduction in glomerular filtration and the smaller diminution of tubule functional capacity that favors a relatively greater percentage reabsorption of electrolytes and water by the renal tubules. This process may be anticipated to contribute to an increasing percentage reabsorption of the glomerular filtrate leading to the accumulation of fluid in tissues and, ultimately, in body cavities.[1,2] The same net effect would obtain under circumstances where glomerular filtration rate is not necessarily diminished but where there is more than commensurate reabsorption of electrolytes, as under the influence of increased production or administration of salt-retaining steroids.[3]

Where there is such an unfavorable imbalance between glomerular filtration and reabsorption of water and electrolytes, the diuretic agent is employed to reduce renal tubular reabsorption of water and sodium (chloride) so as to permit a return to a more suitably homeostatic net balance of function within the nephron(s), even though

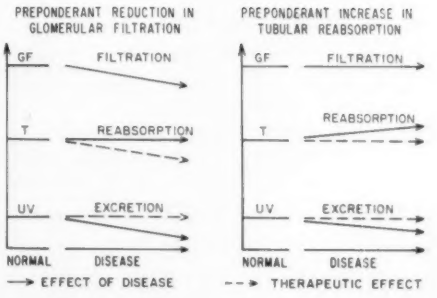

Fig. 1.—Effect of renotropic agents on the excretion (*UV*) of electrolytes and water that has been diminished by glomerulo- (*GF*) tubular (*T*) imbalance.

there be present a marked reduction in glomerular filtration. This reduction in the reabsorption of fluid and electrolytes may be induced by a withholding of water from reabsorption on a passive osmotic basis or by an active reduction in the tubular transport (reabsorption) of critical cations or anions.

The purpose of this presentation is to define the fundamental actions of a number of the available classes of nonmercurial diuretic agents and to comment on their therapeutic application. Within the past few years we have witnessed an upsurge of interest and progress in this phase of pharmacology that is gratifying, considering the critical role renal function plays in the most important field of cardiovascular diseases.

The adjective *diuretic* will be employed where primary consideration pertains to increased urine volume without regard for its composition. The term *saluretic* will be employed to indicate a primary increase in excretion of, predominantly, sodium and chloride. Under conditions of fluid retention a saluretic agent may induce diuresis.

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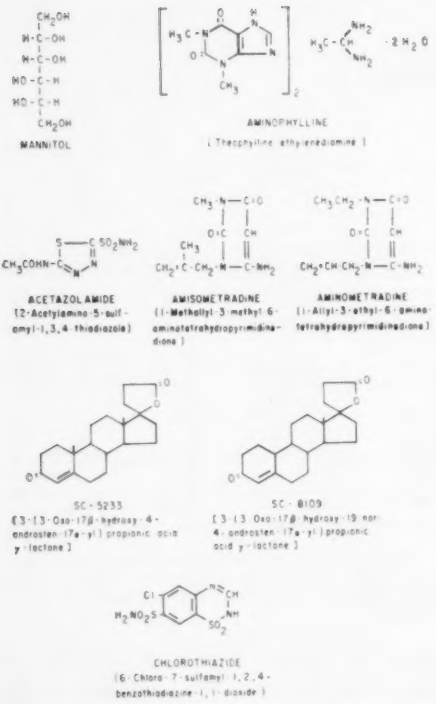

Fig. 2.—Structural formulae of compounds mentioned in text.

I. Osmotic Diuretic Agents

In general, (organic) compounds that are filtered by the glomeruli and not reabsorbed to any great extent by the renal tubules may be shown to exert a diuretic effect. Two examples of such agents that immediately come to mind are urea and the hexahydric alcohol, mannitol (Fig. 2). Such compounds exert their diuretic action by withholding from reabsorption an approximate osmolar equivalent of water.[4,5]

This principle can be illustrated by such an experiment as is represented in Table 1. In these clearance experiments on trained unanesthetized dogs, a control phase was obtained wherein the amount of sodium, potassium, and chloride excreted; urine flow; glomerular filtration rate; urinary pH, etc. were estimated. Thereafter, a very large dose of mannitol, 300 mg. per kilogram intravenously, was administered, and 10 gm. of the agent was given by gavage. It may be seen that, under these circumstances, there was a real increase in urine flow induced by mannitol. It is further evident that in this experiment the osmotic diuretic agent did not cause an increase in the excretion of sodium, potassium, or chloride wherein these ions were measured. Indeed, these experiments are more representative than typical, in the sense that frequently there may be some increase in electrolyte excretion under these circumstances.[5,6] In these experiments the insignificant increase in glomerular filtration rate was insufficient to account for the increase in urine flow.

Organic osmotic diuretic agents are not employed frequently clinically, at least in dosages that would induce a profound effect. In the instance of mannitol, the large dosage, short duration of action, and practical difficulties in administration preclude its wide acceptance, and these considerations would obtain as well for inulin, sorbitol, etc.

TABLE 1.—*Diuretic Effect of Mannitol* *

		H_2O		Sodium		Potassium	Chloride	
	GFR, Ml/ Min.	UV, Ml/ Min.	% Reabsorbed	UV, μEq/ Min.	% Reabsorbed	UV, μEq/ Min.	UV, μEq/ Min.	Urine pH
Dog 295; wt. 24.5 kg.; Exp. 2283								
Control phase: Av. values for three 10 min. clearance periods	68.9	0.28	99.8	5	99.9	14	0.4	6.0
Mannitol: 300 mg/kg. I. V.+10 gm. P. O.	71.9	1.6	97.8	3	99.9	16	1.6	6.0
Dog 604; wt. 21.9 kg.; Exp. 8103								
Control phase: Av. values for three 10 min. clearance periods	68.2	0.30	99.5	39	99.7	32	--	7.4
Mannitol: 600 mg/kg. I. V.+10 gm. P. O.	70.2	1.7	97.6	37	99.5	35	--	7.1

* GFR indicates glomerular filtration rate; UV, amount excreted.

Usually, circumstances where diuretic therapy for serious edema has been indicated have precluded the administration of large amounts of urea for this purpose.

II. Xanthine Diuretics

The action of xanthine diuretic agents is typified by that of theophylline ethylenediamine, which is the most frequently employed of this group. The chemical structure of the compound is included in Figure 2. Xanthine diuretics are among the most intensively studied and least understood of nonmercurial organic compounds. Their effect appears to be primarily one of inhibiting the renal tubular reabsorption of sodium and chloride.[7-10] The diuretic effect probably is secondary to their saluretic action.

An experiment that typifies the action of theophylline ethylenediamine is presented in Table 2. In this instance, it may be seen that large dosages of the compound can induce a marked increase in the excretion of sodium and chloride, secondary to an inhibition of their reabsorption. Undoubtedly, such a change in urine flow as attends the saluretic effect of this compound is secondary to the decreased reabsorption of electrolyte, as illustrated in this Table.

Table 2 also presents one of the attributes of xanthine diuretics that has confused the issue on their mode of action for many years. It may be seen that the compound induced a substantial increase in glomerular filtration rate.[11,12] Whereas at one time the increased glomerular filtration rate was considered to account for the diuretic effect of xanthines, this is no longer held to be their primary attribute.[13,14]

This same experiment (Table 2) shows, in the drug phase, that the saluretic action persisted, even though the glomerular filtration rate progressively decreased to less (39.7 ml. per minute) than that which obtained in the control phase. In this regard the experiment reproduces the observations of Cushny and Lambie [15] published in 1921 and reaffirmed by Walker and his associates.[16]

The inherent potency of the xanthine diuretic agents available to date has not been sufficiently great, nor has their duration of action been adequate for them to be uniformly useful in the correction of the edematous state attending cardiac decompensation. Under these circumstances, adjunctive therapy has been necessary. Thus, in general, they have been least useful where most seriously needed.

III. Pyrimidinediones or Aminouracil Derivatives

Within the past few years two new compounds have been made available which may be considered as pyrimidinediones or aminouracil derivatives. The chemical structures

TABLE 2.—*Theophylline Ethylenediamine Effect on Water and Electrolyte Excretion* *

		H_2O		Sodium		Potassium	Chloride	
	GFR, Ml/ Min.	UV, Ml/ Min.	% Reabsorbed	UV, μEq/ Min.	% Reabsorbed	UV, μEq/ Min.	UV, μEq/ Min.	Urine pH
Dog 601; wt. 16.0 kg.; Exp. 7190								
Control phase †: (500 ml. H_2O, 95 min.; 500 ml. H_2O, 35 min. prior to first clearance)	44.4	5.5	87.6	59	99.2	50	12	7.1
	44.6	5.5	87.7	67	99.1	34	11	7.1
	45.0	5.8	87.2	78	98.9	31	16	7.1
Theophylline ethylenediamine †: Prime 25 mg/kg. I.V.; maintenance 30 mg/kg/hr. I. V. (total dose=933 mg.)	62.8	7.7	87.7	678	95.4	64	530	7.3
	55.6	5.0	91.0	437	95.2	48	218	7.4
	39.7	3.5	91.2	224	96.5	36	170	7.4

* GFR indicates glomerular filtration rate; UV, amount excreted.

† Individual values are for successive 10 min. clearances.

TABLE 3.—*Aminometradine Effect on Electrolyte and Water Excretion* *

	Sodium		Potassium	Chloride	Urinary		
	UV, μEq/Min.	% Reabsorbed	UV, μEq/Min.	UV, μEq/Min.	pH	Flow, Ml/Min.	GFR, Ml/Min.
Dog 751; Exp. 3155; drug dosage 6.25 mg/kg. I. V. prime, 7.5 mg/kg/hr. by venoclysis							
Control	33	99.5	14	22	5.47	7.0	49.8
Drug phase	66	99.0	6	33	5.76	7.0	50.2
Dog 784; Exp. 3185; drug dosage 25 mg/kg. I. V. prime, 30 mg/kg/hr. by venoclysis							
Control	52	99.2	22	15	6.45	6.4	46.5
Drug phase	72	98.9	15	28	6.48	2.6	46.4

* All values are averages of triplicate successive 10 min. clearance periods. UV indicates amount excreted; GFR, glomerular filtration rate.

of the representative agents, aminometradine * and amisometradine,† are presented in Figure 2. Like the xanthine diuretic agents, these compounds inhibit particularly the renal tubular reabsorption of sodium and chloride, as represented by the experiment illustrated in Table 3 with aminometradine. Since the inherent potencies of aminometradine and amisometradine are sufficiently similar, the first of the two agents may be taken to represent the actions of both agents. Here, it may be seen that the preponderant effect of the agent is the inhibition of sodium reabsorption. The effect on chloride excretion is less marked. These agents do not appear to influence glomerular filtration in the dosage employed. In acute experiments such as these, it best can be appreciated that the diuretic action of such agents is secondary to their effects on electrolyte reabsorption. Frequently in such short-term studies there may be a marked increase in electrolyte excretion without any increase in urine flow.

Kattus et al.[17] were the first to lend clinical confirmation to the diuretic action of aminometradine, and their observations were corroborated by Caccamo, Pringle, and Hissong.[18] Clark and Hagans,[19] Wainfeld, Harvis, and Frankhauser,[20] and Watson and Balfour [21] have confirmed the action of the agents in nonedematous subjects and their utility under clinical conditions. Primarily, the drugs are useful for the maintenance of an edema-free state in patients requiring diuretic therapy. In the less severe cases of congestive failure they may effect an initial diuresis. They may be employed to reduce the number of injections of parenterally administered diuretics required in patients with unusual propensities for edema formation. Ford and his associates [22-24] have compared the diuretic activity of these compounds with the other newer diuretic agents in man. Judging by the clinical literature, the incidence of anorexia, nausea, and gastric irritation induced by these agents is the principal type of side-effect that influences their acceptance by the patient. These side-effects are less apt to occur and are less annoying for amisometradine.

IV. Carbonic Anhydrase Inhibitors

The renal tubules contain substantial amounts of carbonic anhydrase.[25] This enzyme, it will be recalled, is responsible for the catalytic reversible hydration of carbon dioxide, which process is critical to the transport of carbon dioxide in the erythrocyte and its exchange in the parenchyma of the lungs. Berliner and Orloff [26] have recently published an excellent review of the role of carbonic anhydrase and its inhibition

* Mictine is the trade-mark of G. D. Searle & Co. for 1-allyl-3-ethyl-6-aminotetrahydropyrimidinedione, the generic name of which is aminometradine.

† Rolicton is the trade-mark of G. D. Searle & Co. for 1-methallyl-3-methyl-6-aminotetrahydropyrimidinedione, the generic name of which is amisometradine.

from a basic and a clinical standpoint. Mann and Keilin [27] reported that organic compounds containing a free sulfamyl group could inhibit carbonic anhydrase in vitro. Höber [28] first indicated that the enzyme was somehow associated with the acidification of urine. Pitts and his associates [29] accounted for urine acidification on a hydrogen-for-sodium ion exchange across the luminal border of the renal tubule, hydrogen ions being made available through the intermediation of carbonic anhydrase. Schwartz [30] made the first therapeutic application of the inhibition of renal carbonic anhydrase by sulfanilamide. He reported it to increase sodium and fluid excretion in edematous patients, but the toxicity of the compound precluded its general use for this purpose.

The first of the clinically safe and useful carbonic anhydrase inhibitors to be employed as a diuretic agent was acetazolamide‡ (Fig. 2). Its pharmacology was thoroughly explored by Maren and his associates.[31,32] It remains today one of the more potent carbonic anhydrase inhibitors, in vitro.

Acetazolamide is well absorbed when administered orally; the duration of action is at least 6 to 12 hours. Its renal clearance is estimated to be about two-thirds of glomerular filtration rate. It is widely distributed and can be shown to inhibit carbonic anhydrase in the erythrocyte, the eye, the brain, the stomach, and the pancreas. Thus, it is effective in the management of glaucoma [33] and some types of epilepsy.[34,35]

In general, acetazolamide induces a natriuresis which is attended by a marked increase in potassium and especially bicarbonate excretion.[31,32,36] The typical renal effects of the drug are represented by the clearance experiments presented in Table 4. Most characteristic is the increase in sodium and bicarbonate excretion, thus causing an increase in urinary pH. The decreased glomerular filtration rate is usually seen in acute clearance experiments following intravenous but not subsequent to oral administration. It is noteworthy that acetazolamide does not cause an increase in chloride excretion of any consequence.

Presumably due to the initial marked increase in bicarbonate excretion, metabolic acidosis and refractoriness to the renotropic effect of the drug develop. This may occur in a few days time if high dosages are administered daily. Also, acidosis induced by the administration of ammonium chloride, which is employed commonly as an osmotic diuretic agent, diminishes or abolishes responsiveness to the compound.

‡ Diamox is the trade-mark of the American Cyanamid Co. for 2-acetylamino-5-sulfamyl-1,3,4-thiadiazole, the generic name of which is acetazolamide.

TABLE 4.—*Acetazolamide Effect on Electrolyte and Water Excretion* *

	Sodium		Potassium	Chloride	Urinary		
	UV, μEq/Min.	% Reabsorbed	UV, μEq/Min.	UV, μEq/Min.	pH	Flow, Ml/Min.	GFR, Ml/Min.
Dog 606; Exp. 5194; drug dosage 1.0 mg/kg. I.V. prime, 1.5 mg/kg/hr. by venoclysis							
Control	44	99.5	22	7	6.2	2.1	65.1
Drug phase	183	97.8	82	30	7.5	5.4	61.5
Dog 606; Exp. 534; drug dosage 2.5 mg/kg. I. V. prime 3.0 mg/kg/hr. by venoclysis							
Control	61	99.3	14	19	6.3	3.0	68.3
Drug phase	314	96.1	76	65	7.9	4.8	59.9
Dog 291; Exp. 1142; drug dosage 25 mg/kg. I. V. prime, 30 mg/kg/hr. by venoclysis							
Control	46	99.5	43	21	6.7	8.1	60.6
Drug phase	307	94.8	145	18	8.8	3.8	42.0

* All values are averages of 2 or 3 successive 10 min. clearance periods. Ratio of drug dosages in the experiments in increasing order was ca 1:2:20. UV indicates amount excreted; GFR, glomerular filtration rate.

Although the compound has met with generally favorable acceptance, its efficacy as a diuretic for the patient with severe heart failure has been satisfactory in some but inadequate in other instances.[37-39] Counihan et al.[40] and Leaf and his associates [41] have attributed its limited diuretic usefulness in the maintenance of some edematous patients to the sharp limitation of reduction of extracellular fluid that can be induced by the increased excretion of bicarbonate (without chloruresis). However, once the patient is brought under control by adjunctive therapy the use of acetazolamide alone may be satisfactory.

In the application of acetazolamide to therapeutic problems, it has been proposed that the compound be given in small daily dosages or in larger amounts on an interrupted schedule to obviate the development of refractoriness to the agent. In general, the side-effects of acetazolamide are attributable to its effect on the carbonic anhydrase activity of the central nervous system. These include paresthesias and drowsiness that are reversible by withdrawing the medication.

V. Steroid Antagonists

As the role of aldosterone in the pathogenesis of fluid retention associated especially with cirrhosis, nephrosis and, to less extent, hypertensive cardiovascular diseases has become better understood,[3,42-44] there has been increasing interest in the development of antagonists to the renotropic effect of this and other corticosteroids. It will be recalled that aldosterone and the principal corticosteroids influence the reabsorption especially of sodium (chloride) and, in this way, increase the retention of fluid, either on an endogenous or an iatrogenic basis. Thus, a compound that could antagonize the salt-retaining attribute of aldosterone or mineralocorticoids generally, and which would not possess the other pharmacodynamic attributes of these agents, would be of potential utility. A step in this direction has been made recently at a preclinical level by Kagawa et al.[45] and in a clinical evaluation by Liddle.[46] In these studies it was shown that two steroids (SC-5233 and SC-8109), the structures for which are represented in Figure 2, were capable of antagonizing the action of aldosterone or deoxycorticosterone in the rat and of deoxycorticosterone in man. Our studies on compounds such as SC-8109 indicate that in the normal or the adrenalectomized dog they do not act per se to increase salt excretion. Whether or not these particular compounds are sufficiently attractive for general use, they will have served admirably to indicate that this approach to the regulation of electrolyte excretion is worthy of investigation.

VI. Chlorothiazide

Although the structural formula presented for chlorothiazide § in Figure 2 characterizes it as a potential carbonic anhydrase inhibitor, its over-all renotropic effect differs markedly from that of acetazolamide. Indeed, it appears to be intermediate in its pharmacodynamic characteristics between acetazolamide and the organomercurial diuretic agents. Thus, the compound causes a marked increase in the excretion of sodium chloride and less effect on potassium and bicarbonate.[47-50] These characteristics are illustrated by the experiment represented in Table 5. From both a fundamental and a practical standpoint, this agent has been particularly interesting because of its efficacy under a wide range of circumstances such as obtain in clinical therapy. This is illustrated by the set of experiments presented in Table 6. In the first of these experiments, a dog was maintained on a very low sodium intake prior to the experiment. Even so, chlorothiazide caused a very definite saluretic effect.

§ Diuril is the trade-mark of Merck & Co., Inc., for 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide, the generic name of which is chlorothiazide. A second more potent, but qualitatively similar, compound is 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide, the generic name of which is hydrochlorothiazide. HYDRODIURIL is the trademark of Merck & Co., Inc. for this latter compound.

TABLE 5.—*Protocol and First Clearance Experiment Pertaining to Effect of Chlorothiazide on Electrolyte Excretion by the Dog* *

Time, Min.	Sodium UV, μEq/Min.	Sodium % Reabsorbed	Potassium UV, μEq/Min.	Potassium Net % Reabsorbed	Chloride UV, μEq/Min.	Urinary pH	Urinary Flow, Ml/Min.	Creatinine Clearance, Ml/Min.
-60	500 ml. water, P.O.							
-30	500 ml. water, P.O.							
-20	3.0 gm.creatinine, subcutaneously; 1.5 mg/kg. 0.14 M phosphate I. V. prime, and venoclysis of 0.023 M PO_4 containing 0.23 M mannitol at 3 ml/min. (pH 7.41)							
Control phase								
0-10	8	99.7	14	84.1	6	5.8	1.5	25.8
10-20	6	99.8	12	89.7	5	6.0	1.0	35.7
20-30	8	99.8	13	87.1	4	6.0	0.9	32.7
Chlorothiazide phase: 6.25 mg/kg. I. V. prime+7.5 mg/kg/hr. in PO_4-mannitol venoclysis (pH 7.53)								
50-60	285	93 8	55	44.7	134	7.9	2.4	33.8
60-70	311	93.6	55	46.8	142	7.9	2.7	36.1
70-80	241	93.7	42	48.9	119	7.9	2.1	28.2

* Dog 804; wt. 14.1 kg. UV indicates amount excreted.

In the second experiment, Table 6, ammonium chloride was administered in sufficient amounts to cause a marked acidosis. In such experiments the compound caused an increase in excretion of chloride that exceeded the excretion of cations sufficiently to cause a decrease in urinary pH, there being essentially no effect on bicarbonate excretion. Under conditions of high sodium chloride intake, chlorothiazide caused a profound saluresis with little or no change in urinary pH. On the other hand, when dogs were made alkalotic by the administration of large amounts of sodium bicarbonate, chlorothiazide caused a profound increase in the excretion of bicarbonate along with the natriuresis, the proportion being such as might be presumed to induce a more favorable homeostatic acid-base balance.[51] It will be recalled that under conditions both of low salt intake and acidosis the patient or dog becomes refractory to the effect of acetazolamide [31,32] and that the organomercurial diuretic agents are less effective under conditions of alkalosis.[52,53]

The fact that the pharmacodynamic effects of this agent appear to be limited to its renotropic action has been an important factor in the low incidence of side-effects. Indeed, the ability of the homeostatic mechanisms of laboratory animals to maintain good electrolyte balance and general

TABLE 6.—*Effect of Low-Salt Diet and of Salts* * on the Saluretic Action of Chlorothiazide† in Dogs*

	Na^+ μEq/Min.	Na^+ % Reabsorbed	K^+ μEq/Min.	Cl^+ μEq/Min.	HCO_3^- μEq/Min.	Urine pH	Creatinine Clearance, Ml/Min.	Plasma pH
Low-salt diet								
Control	1	99.99	14	3		5.60	73.0	
Drug	323	96.85	73	121		7.80	71.8	
Ammonium chloride								
Control	18	99.8	34	80	2	5.26	57.5	7.23
Drug	200	97.5	53	320	6	4.70	57.1	
Sodium chloride								
Control	84	98.5	16	12	25	6.86	45.3	7.45
Drug	443	92.6	56	324	71	7.19	42.6	
Sodium bicarbonate								
Control	212	97.8	38	9	182	7.91	64.8	7.57
Drug	598	92.8	78	194	415	8.03	55.5	

* 100 mEq/day P. O. for 5 days.
† 2.5 mg/kg. prime; 3.0 mg/kg/hr. I. V.

welfare in spite of the protracted administration of exorbitant amounts of the compound intravenously or orally is impressive.[54] Although the compound can be demonstrated to be saluretic for dogs at a dosage of 0.05 mg. per kilogram intravenously, they tolerate well the daily intravenous administration of 500 mg. per kilogram over a period of weeks. Likewise, the oral administration of 1000 mg. per kilogram daily for weeks is well tolerated by dogs. Smaller but excessive dosages have been administered to laboratory animals for many months. The only noteworthy response after the initial saluresis in these experiments has been the development of a hypokalemia that has not been apparent except by plasma values. The hypokalemia has been noted clinically as well.[55] The physician should be aware that hypokalemia may occur, particularly under combined conditions of enthusiastic salt restriction and high maintained chlorothiazide dosage.

Clinically chlorothiazide is widely effective, and it appears to be safe for protracted administration. Its utility has been extended to those conditions that can be benefited from its effects on electrolyte balance. Thus, where there is serious retention of salt and water, such as in cardiac decompensation, cirrhosis, nephrosis,[56-61] and the edema of pregnancy,[62] the saluretic effect may cause a profound diuresis and weight loss. In a comparison with other important agents referred to herein, Ford[24] has considered it to be superior on the basis of continuous efficacy, relative freedom from biochemical disequilibrium, comparative potency, and convenience or economy to the patient. The compound has been reported to be of use in the basal management of hypertensive patients, supporting or lessening the requirements for more stringent measures,[63-67] even though the patient is not edematous. This latter effect is considered by the author to be based on the role of less than obvious salt retention in the pathogenesis of certain cardiovascular (hypertensive) diseases. In addition, I have entertained the hypothesis that chlorothiazide may influence the distribution of sodium and potassium across the cell membrane of the vascular muscularis, as that relationship may be supposed to contribute basically to tonus of the arterioles and the maintenance of blood pressure.

The mode of action of chlorothiazide appears to be complex, whether or not it will prove to be so, basically. Although several investigators have approached this problem from their own points of view, there is agreement that the agent differs importantly from acetazolamide and the organomercurials.[68-70]

Summary

In general, the organic osmotic diuretic agents are of little use in serious circumstances except as adjuncts to other diuretic therapy.

Whereas the xanthines may be useful as adjuvants to the intermittent use of more effective organomercurial therapy, they are usually inadequate for the maintenance of the frankly edematous patient.

The aminouracils have been employed satisfactorily for the maintenance of therapy once the edematous severely decompensated patient has been brought under control.

Although it is commonly thought that natriuresis is adequate to evoke the loss of substantial water and weight from the edematous patient, it seems clear now that the anion preponderantly excreted along with sodium may be a limiting factor in the utility of diuretic agents. Thus, acetazolamide increases the excretion of (sodium) bicarbonate, predominantly. If the full natriuretic effect of the agent is exercised in therapy, the excretion of bicarbonate over a period of a few days of continuous administration may be sufficient to induce a metabolic acidosis, under which conditions the agent is relatively ineffective. It has been recommended that this drug be given at low dosage on a continuous schedule or intermittently at higher dosages.

Chlorothiazide appears suitable for the therapy of numerous classes of edema.

When administered orally, its utility approximates that of the presently available parenterally administered mercurials.[23,24]

Merck Sharp & Dohme Research Laboratories.

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Mercurial Diuretics

Their Mechanism of Action and Application

C. THORPE RAY, M.D., Columbia, Mo.

The origins and development of mercurial diuretic therapy have been reviewed extensively in recent years.[1-5] The mercurial diuretics have been subjected to much clinical testing and investigation over the past 35 years and have been shown to be potent, dependable, and of relatively low intrinsic toxicity. The addition of theophylline resulted in reduced local reaction at the site of injection and an increase in the diuretic potency.[6] Additional reduction of cardiovascular toxicity was achieved by substituting a thiol group to produce a mercaptomercurial.[7-9] A number of modifications in the molecule have resulted in new names, but there is no appreciable difference in the diuretic potency of the various injectable preparations of organomercurials currently available. Since the pharmacodynamics of the organomercurials is the same for all preparations, the following brief review of mechanism of action applies to all of the mercurial diuretics, both oral and parenteral.

For any compound to produce a diuresis there must be some renal effect. Tubular reabsorption must be reduced either in absolute amounts or in relation to glomerular filtration. Since there is abundant evidence that the organomercurials do not increase glomerular filtration, their effect must be on tubular function.[4,10,11] The site of action on the renal tubule has been the subject of considerable investigation and dispute.[3-5] Depending on the assumptions made in treating the data, it has been possible to localize the effect in the proximal tubule in some instances and in the distal tubule in others. Recently, both Weston[12] and Pitts[10] have concluded that the site of action of mercury is the proximal tubule. However, these data do not exclude some distal tubular action as well. Certain proximal tubular functions are known to be influenced by therapeutic doses of mercurials; such functions include secretion of iodopyracet (Diodrast) and *p*-aminohippurate and reabsorption of uric acid, calcium, and glucose. These findings and the fact that minimal necrotizing doses of mercury localize in the proximal tubule give weak support to the idea of proximal tubular action of mercurial diuretics. Whereas the distal tubular functions of acidification and ammonia secretion are not influenced by mercurial diuresis, the secretion of potassium, which is clearly a function of the distal tubule, is affected. Final and conclusive proof on the site of action is not yet available.

In addition to the inconclusive data as to the site of action of mercurial diuretics in the renal tubule, the mechanism by which mercury causes its characteristic effect on the tubular cells is likewise unknown. Mercury is known to have a strong affinity for sulfhydryl groups, and it is known that there is a high concentration of sulfhydryl groups in the kidney, particularly in the enzyme succinic dehydrogenase.[10,11,13] Large doses of mercury reduce the succinic dehydrogenase activity in the rat kidney.[13] Furthermore, a relation between diuresis and the reduction in succinic dehydrogenase activity is demonstrable. The renal content of suc-

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cinic dehydrogenase is normal after recovery from mercurial diuresis as well as after administration of dimercaprol. More sensitive techniques have shown a reduction in the amount of protein-bound sulfhydryl following ordinary clinical doses of mercurials.[14] If mercurial diuresis is dependent on inactivation of sulfhydryl-containing enzymes, all compounds which inactivate these enzymes should result in a diuresis. However, in a study of some 13 mercurial compounds, 6 of which were diuretic and 7, nondiuretic, the renal binding of the mercury did not separate the diuretic from the nondiuretic compounds.[15] All compounds, regardless of diuretic properties, were concentrated in the kidney. Three of the nondiuretic compounds were potent succinic dehydrogenase inhibitors, and one of these three, *p*-chloromercuribenzoate, was excreted as rapidly as the diuretic compounds. The authors proposed a certain molecular configuration which was necessary for diuretic effects, with a lock-and-key fit with a receptor to explain the mechanism of action. This hypothesis does not explain the diuretic effect of inorganic mercurials and certain diuretic organomercurials which do not have this molecular configuration.[11] Although the transport of strong electrolytes which is influenced by mercurial diuretics may be the result of some active cellular process, the current techniques of enzyme chemistry are not able to identify the precise mechanism or enzyme system involved in mercurial diuresis.

For mercurials to produce diuresis there must be some reversible interaction between mercury and some cellular component. Whether this interaction is between the mercury ion or the intact organomercurial compound and this cellular constituent is not known. The findings of Moyer and associates indicated that the organomercurial compound was excreted in the urine still intact.[16] The significance of his finding has been questioned, since the technique of identification used would not distinguish the parent organic diuretic molecule from that of mercury complexed with cysteine,[11] which is the form in which most inorganic mercury is excreted in the urine.

In addition to the uncertain knowledge about the site of action and precise mechanism of action of the mercurial diuretics, the primary effect of mercurial diuretics on tubular function was considered by some to be chloruretic and by others to be natriuretic.[4,13,14,17,18] The primary chloruretic effect was suggested by finding chloride in excess of sodium during mercurial diuresis. The excretion of bicarbonate was not increased, and this was used as an argument against the primary natriuretic effect of mercurials. If one assumes that the site of action of a mercurial diuretic is on the proximal tubule, it is then possible to explain why the urine contains more chloride than sodium. With inhibition of reabsorption in the proximal tubule more sodium and chloride escape into the "uninhibited" distal tubule, where removal of sodium through exchange for hydrogen, potassium, and ammonium results in the excess of chloride. In this manner the mercurial diuretics may be primarily natriuretic and yet the urine will contain more chloride than sodium.

The responsiveness to a mercurial diuretic may be conditioned by a number of factors. It has been shown that ammonium chloride administration may potentiate the diuretic effect of mercurials.[17,19,20] This effect has been ascribed to increased acidity of body fluids, to increased acidity of the urine, and to the altered anion pattern in the blood plasma, particularly the increase in the concentration of chloride in plasma so that a greater load of chloride is filtered.[17] When inhalation of carbon dioxide produced the same degree of acidosis as the administration of ammonium chloride yet did not potentiate the effect of mercurials, these authors felt that the pH alone was not as important as the filtered load of chloride. Additional studies have thrown some doubt on the idea that the concentration of chloride in the plasma is the only important factor. Hilton has shown that the potentiating effect of am-

monium chloride is continued even after the chloride in the plasma returns to normal concentration.[21] In additional studies, Mudge and associates have shown that whereas the infusion of bicarbonate results in a decrease in plasma chloride and inhibits the effect of mercury, a similar depression of chloride in the plasma from infusion of sodium nitrate does not inhibit the diuretic effect of mercurials.[11,20] Furthermore, in chronic hypokalemic alkalosis, with hypochloremia, there was no inhibition of mercurial diuresis. In this condition there is an acid urine, an alkalosis in the extracellular fluids, and an intracellular acidosis. Since the action of mercurial diuretics in these circumstances seems to be influenced by factors other than the level of serum chloride, the role of pH in conditioning the response to mercurial diuretics should be considered. There are additional reasons to suspect that the pH of the environment may affect the diuretic action of the mercurials. The organomercurials are more unstable in an acid medium,[11] and, furthermore, the affinity of mercury for sulfhydryls is influenced by an acid medium.[22]

In addition to the influence of plasma chloride and pH on the action of a mercurial diuretic, a marked effect of low glomerular filtration rates is demonstrable.[12,23,24] With very low filtration rates, such as may be encountered in severe heart failure, the reabsorption of the filtrate may be so nearly complete in the proximal tubule, even with mercurial inhibition of reabsorption, that the distal tubule is able to reabsorb practically all of the diminished sodium load delivered to it. In instances where the filtration rate was markedly reduced without any change in tubular function, even during a mercurial diuresis, there was a reduced excretion of sodium.[24]

The foregoing remarks have been directed entirely toward the action of mercury on the kidney. There is important evidence that the effect of mercurial diuretics can be explained on renal action alone. Such observations consist of injection of mercury into one renal artery with subsequent diuresis only from the kidney into which the mercury was injected.[25] When the amount of mercury injected was increased, diuresis occurred from both kidneys, and when the dose was increased still further, the kidney into which the mercury was injected failed to respond, while the opposite kidney manifested a diuresis. Recently this type of experiment was repeated.[10] In this instance the kidney into which mercury was injected showed an immediate diuretic effect. However, some of the mercurial gained access to the general circulation and was extracted and excreted by the right kidney. It is extremely interesting that when the right kidney had extracted and excreted as much mercury as had the left one when the latter was undergoing diuresis the right kidney still had shown no effect of the mercurial. Although the right kidney began excreting mercury almost as soon as the left one there was no diuresis from the right kidney until more than an hour had elapsed after the injection. After that time the right kidney manifested the usual effects of a mercurial diuretic. This finding is difficult to explain on the basis of renal action of mercury alone.

After an intravenous injection of a mercurial diuretic there is a very rapid decline in the concentration of the mercurial in the serum.[26] This decline in concentration in the serum after the first 40 to 50 minutes following the injection is predictable on the basis of urinary excretion, indicating the continued renal extraction of mercurial compounds from the plasma. Simultaneous observations of renal, hepatic, and extremital extraction of a mercurial diuretic indicated that initially there is a considerable amount of mercury not accounted for by the content of mercury in the plasma, kidneys, and urine.[27] Over 50% of the mercury had been lost from the plasma by 15 minutes after injection. The part of the injected mercury which was calculated to be in the "tissues" gradually declined with time, and after a short time the concentration of radiomercury in the hepatic and extremital veins ap-

proached or exceeded the arterial concentration, indicating a release of mercury back into the circulation. Although studies of the distribution of a radiomercury-labeled mercurial diuretic indicated that little of the radiomercury remained in the tissues,[28] there is a significant amount in the tissues for a short time after injection. That this part of the mercurial diuretic which is in the tissues is influencing the diuresis is not known, but certainly an effect is not excluded.

Another interesting feature of these acute experiments was the antidiuresis noted in a number of subjects.[27] This period of antidiuresis lasted as long as 90 minutes, and it occurred during the time when concentration of the mercury was highest in the urine. In previous experiments with direct injection into the renal artery there was no delay in the onset of diuretic action.[25] Therefore it would not seem necessary to postulate that the mercury in the organic molecule needs much modification before it becomes pharmacologically active. In view of these findings, one can not help questioning how definitely extrarenal actions of mercurial diuretics have been excluded.

In spite of the many unknown features about the mechanism of action of the mercurial diuretics on the kidney, the clinical effects of mercurial diuresis on the volume and constituents of the urine and body fluids is well known. There is an increase in urinary excretion of sodium, chloride, and water, while the effect on the excretion of potassium is variable. Since mercurial diuretics result in the removal of salt and water from the body, it follows that this class of drugs is most useful in diseased states characterized by accumulations of excess fluid and electrolytes, particularly congestive heart failure, the nephrotic syndrome, and cirrhosis of the liver with ascites. Since the greatest clinical application of mercurial diuretics is in congestive heart failure, the application of mercurial diuretic therapy in this syndrome will be given the most consideration. In all of these diseased states the kidney has retained salt and water with a normal intake. This behavior of the kidney is secondary to the primary disease, and therefore when one is treating the fluid accumulations alone the therapy is *secondary*. In congestive heart failure *primary* therapy is directed toward improving the circulation by such measures as administration of digitalis, correcting the underlying etiology (anemia, hyperthyroidism, etc.), or reducing circulatory demands so that circulatory capacity can meet demands. When such measures are inadequate or are not applicable then drugs are employed whose function is to remove the excess fluid and electrolytes. The removal of edema fluid may be more than symptomatic therapy, since the demands on the circulation may be affected indirectly. For example, relief of pulmonary congestion reduces the muscular effort of respiration with congested lungs. It should be emphasized that diuretic therapy with any of the currently available diuretics is in great part secondary therapy and should not be allowed to distract from the primary therapy directed toward the basic disease state.

The role of the mercurials in the management of congestive heart failure is well established. The extensive clinical experiences gained over the past 35 years have shown that the mercurial diuretics are potent. In patients with mild and moderately severe congestive heart failure the response to the mercurial diuretics is usually good and continues so for long periods of time. In some instances of mild congestive heart failure the institution of diuresis by the mercurials will result in continued spontaneous diuresis. However, it is unfair to attribute this response entirely to the beneficial effects of mercurials alone, since spontaneous diuresis in patients with mild and moderately severe heart failure is not uncommon following removal of the factors which increase the circulatory burden and thus precipitate the episode of decompensation. In other instances the loss of extracellular fluid volume by mercurial diuresis results in a stronger salt-retaining tendency. By comparing the

daily excretion of sodium before and after mercurial diuresis it can be shown that there is an added retention of sodium and chloride in the period following diuresis. This is true both in normal subjects and in patients with congestive heart failure. This increased tendency to retain salt and thus to defend the previous steady state of fluid volume may be due to increased secretion of salt-retaining steroids from the adrenal gland, although it is not clear how a change in volume stimulates the adrenals.

At the onset of mercurial diuretic therapy for congestive heart failure the parenteral route of administration is usually necessary. In some instances of mild heart failure the oral preparations might suffice, but for dependable diuresis in the more severely ill patients therapy should be begun with parenteral injections, preferably not over 1 cc. The ideal dose of mercurial diuretics is the smallest amount which causes the desired response. This dosage can be established only by trial and observation.

Once diuretic therapy has been begun the need for a clear idea of the therapeutic goal of diuresis becomes apparent. At times this goal has been identified as "dry weight," but when one considers that mercurial diuretic therapy is most often secondary or symptomatic, then the asymptomatic state should serve as a reasonable therapeutic goal. The maximal benefit is not attained as long as there is evidence of pulmonary edema or paroxysmal nocturnal dyspnea. In such instances one should try to achieve a state of extracellular fluid volume at which pulmonary distress no longer occurs. In other patients an asymptomatic state may be achieved in the presence of some expansion of the extracellular fluid volume. The support to the circulation from a slight expansion of the body fluids may be more desirable than the disadvantages of a slight amount of dependent edema.

Many years of clinical usage have shown the mercurial diuretics to be potent. In fact, their potency is such that serious depletion of electrolytes and water may follow their use. This is particularly true in disease states, such as congestive heart failure, which are characterized by inadequate homeostasis. The more nearly normal the person, the more vigorous is the defense of osmolarity and volume of the body fluids. It is difficult to deplete a normal person by repeated mercurial diuresis, while depletion states may readily be produced in the patients with severe heart failure. Regulation of the osmolarity and volume of the body fluids is obviously neither precise nor dependable in such patients. The severer the heart failure the less ability there is to adapt or to adjust to rapid changes in the volume or constituents of the body fluids. There is apparently some advantage of an expanded fluid volume in supporting the circulation, and too rapid a reduction in this volume may result in marked weakness, particularly in the upright position. The commoner manifestation of depletion is hypochloremic alkalosis, usually with some hyponatremia as well. The severity of the clinical manifestations usually parallels the severity of the depletion state. Mental confusion, low blood pressure, rising blood urea nitrogen, and ultimately peripheral vascular collapse represent the extreme. In view of the instability of electrolyte metabolism in congestive heart failure plus the finding of continued excretion of mercury in the urine for longer than 24 hours following administration,[29] it is advisable to allow at least a day between injections of mercurial diuretics. This is especially true when the patient has already received several injections. Since the response of an individual patient to mercurial diuresis is usually unknown at the onset of therapy, the use of small doses of mercurials may avoid excessive diuresis. It is advisable to begin with not more than 1 cc.

Although some patients with congestive heart failure experience an excessive diuresis in response to the mercurials, there are many with severe heart failure who are refractory or resistant to its action. This apparent refractoriness to mercury may be present when therapy is first begun or may

ensue only after considerable diuresis has already occurred. In such cases a survey of the electrolyte pattern in the serum may reveal a hypochloremic alkalosis as the cause of the unresponsiveness. Correction of the abnormalities in the electrolytes by administration of ammonium chloride usually restores the response to mercurials. In some of the refractory cases with a normal electrolyte pattern in the serum the mercurials still fail to elicit a diuresis. In such instances the problem should be reviewed from the standpoint of measures and drugs which increase glomerular filtration rate. Aminophylline given intravenously may enhance the diuretic response to mercurials, presumably by increasing filtration rate. The low rate of glomerular filtration which is often encountered in instances of severe heart failure may decrease even more with muscular effort. For this reason bed rest should be advised when attempting mercurial diuresis in severe heart failure. Attention should be given to the burden of thermal regulation, especially in a hot and humid environment. The burden of thermal regulation may be the circulatory equivalent of walking. Thus, providing a comfortable environment and the use of antipyretics in the presence of fever is physiologically sound.

The potentiating effects of ammonium chloride may be used to advantage even in the absence of a hypochloremic state. Effective potentiation of mercurial diuresis may result from continued administration of ammonium chloride even though the diuresis from the acid salt itself lasts only a few days. Preparation of the patient with both ammonium chloride and acetazolamide has been suggested,[30] but this particular combination of drugs may produce a severe hyperchloremic acidosis and therefore should be undertaken only with careful supervision. The presence of a hyperchloremic acidosis is an ideal chemical environment for potentiation of mercurial diuresis. Acetazolamide alone tends to create this chemical environment, although not at the time of its maximal action on the kidney. The combination of chlorothiazide with mercurials may result in a greater loss of weight than the use of mercurials alone. Thus this combination may be useful when either drug alone fails to produce the desired loss of weight.

Even with correction of electrolyte depletion and the use of the potentiating agents with mercurial diuretics there will be instances of severe heart failure in which an adequate diuresis will not result. In such cases a phlebotomy of 500 to 800 cc. followed by a mercurial diuretic may result in a loss of 5 to 10 lb. when other measures have failed. Phlebotomy is most helpful when hypervolemia and increased venous pressure are present. The mechanism by which phlebotomy enhances the action of a mercurial diuretic is unknown, but the effect of bleeding on decongesting the lungs and decreasing the work of respiration may be important in this response. Similarly, an abdominal paracentesis may restore responsiveness to the mercurials.

Once the patient with congestive heart failure is "compensated" there may be no further need for diuretic therapy. However, should diuretic therapy be required to maintain an asymptomatic weight when the patient increases his physical activities and salt intake, then it is necessary to establish a regimen of maintenance therapy. The therapeutic goal is to keep the patient in an asymptomatic state, and the minimal dose of diuretic which accomplishes this is the dose of choice. In mild and moderately severe cases of congestive heart failure satisfactory maintenance therapy may be achieved by the use of oral mercurial diuretics. The convenience of oral administration is apparent when this route suffices to maintain the proper weight. There is a sacrifice in potency and reliability when one changes from the parenteral to the oral preparations.[31] The tendency of all of the oral preparations to produce nausea and gastrointestinal disturbances may prevent administration of adequate diuretic therapy by this route. The severer cases of congestive heart failure

usually require parenteral injections to maintain proper weight. The intervals between injections may be lengthened by the use of oral preparations, but some parenteral therapy is usually necessary.

Providing a small but frequent diuretic stimulus has a greater advantage in maintaining steady weight than an infrequent large dose of diuretic which is administered after the patient has become symptomatic from an excessive volume of extracellular fluid. Small daily diuretic stimuli are obviously much better provided by daily administration of oral mercurial diuretics or by daily injections of small amounts of parenteral preparations which are well tolerated subcutaneously. A regimen of 0.2 cc. of diuretic daily or every other day has been found to be very successful.

As indicated previously, most of the clinical applications of mercurial diuretics will be in congestive heart failure, and for that reason this presentation has dealt largely with this aspect of diuretic therapy. There is a very limited usefulness of mercurial diuretic therapy in cirrhosis of the liver with ascites. Its use is purely symptomatic therapy, but in some instances of cirrhosis with ascites there is good diuretic response and abdominal paracentesis can be avoided or postponed. When hepatocellular function is so reduced that severe hypoalbuminemia is present, then the mercurials are not usually as effective in the control of the ascites.

In the nephrotic syndrome diuretic therapy is often helpful in providing symptomatic relief from the massive accumulations of edema fluid. In this instance, as in cirrhosis with ascites, diuretic therapy is purely symptomatic, since it is not known to have any beneficial effect on the underlying disease process. It is not unusual for the mercurial diuretics to produce a good diuresis initially in the nephrotic syndrome, but they may lose their effectiveness with time even with persistent edema and essentially normal electrolyte values in the serum. Hypoproteinemia, which is an important part of this syndrome, may lessen the effectiveness of the mercurial diuretics. When effective, the mercurials may provide welcome relief from the massive edema of the nephrotic syndrome and should be given an adequate therapeutic trial.

Mercurial diuretic therapy has been used to some advantage in the syndrome of preeclampsia.[32] In response to both oral and parenteral therapy there was loss of edema, lowering of the blood pressure to normal levels, and disappearance of the albuminuria. The use of mercurial diuretics appears to be very helpful in the management of preeclampsia. The importance of these observations must await a better understanding of the syndrome of preeclampsia.

Summary

In spite of many years of clinical usage, there are several aspects of the mechanism of action of the mercurial diuretics which are unknown. The precise manner in which it inhibits tubular reabsorption of sodium and the site of action on the renal tubule are not clearly established. However, these gaps in knowledge do not interfere with the clinical application of this very useful class of drugs. Clinical observation has proven the mercurial diuretics to be potent and reliable diuretic agents.

Department of Medicine, University of Missouri Medical Center.

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An Analysis of the Causal Factors of Atherosclerosis

EDWIN F. HIRSCH, M.D., Chicago

Atherosclerosis of the aorta and of its main arterial branches ranks high among the causes of natural death in man. Although the records and observations of atherosclerosis in man and in lower animals extend far into antiquity, no generally accepted cause for the evolution of the disease has been proposed. Opinions expressed recently [4,5] offer the hypothesis that diets rich in animal fats have a causal relation to atherosclerosis in man. The implied impact of this fat-rich diet on the arterial tissues is through the lipids in transport in the blood and from which the lipids in the fatty plaques of the intima are derived.

Some regard the lesions of atherosclerosis as part of an aging process; others think that they are caused by lipid infiltrations of the intima and result from disorders of lipid metabolism.[2] Each view alone is confronted with pertinent objections. The one view emphasizes a structural change or injury of the blood vessels as an aging process, the other, a dyscrasia of lipid metabolism, with specific emphasis on the cholesterol content of the lipid deposits. The advocates of the second view speak with assurance because rabbits and other animals fed cholesterol develop a form of atherosclerosis which resembles that of the human. They have stressed cholesterol as important, unmindful of the other lipids in the fatty deposits, and have cautioned against diets containing cholesterol, although the tissues of the host synthesize large amounts of cholesterol in normal metabolism. Views now currently in favor [1] consider that two factors, a tissue and a lipid, contribute specifically to the evolution of atherosclerosis, the first if only the medium for the sequences of the second.

The older pathologists,[2] Virchow, Sanders, Beitzke, Wells, and others, believed that the evolution of atherosclerosis depends upon focal injuries or retrogressive changes of the media, commonly ascribed to an aging process. The lesions of the intima according to this view are secondary. The second theory of the cause of atherosclerosis, favored by Marchand, Lubarsch, Aschoff, Anitschkow, and Leary, emphasized the importance of the lipid infiltrations of the intima. The lipid deposits, according to this view, are primary and initiate other changes of the vessel wall, and atherosclerosis is a specific disease in which aging of the tissues is only a contributing factor.

All descriptions of atherosclerosis mention as sequential in its evolution the deposits of lipids, the formation of fibrous and fatty plaques, the occurrence of atheromas, and the deposition of calcium in the lining of the aorta and of its branches as the specific features of the disorder. The initial gross manifestations are the fatty streaks or nodules in the intima of the root, the arch, and the posterior wall of the aorta, especially about the ostiums of the intercostal and other artery branches. Growths of fibrous tissue in the fatty deposits with extension into the media form larger discrete and confluent button-like nodules. Later, with necrosis, the center softens and becomes a soft mixture of lipids and tissue

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From the Henry Baird Favill Laboratory of Presbyterian-St. Luke's Hospital.

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The Seymour Coman Fellows of the Departments of Chemistry and of Pathology of The University of Chicago have made significant contributions to the studies of atherosclerosis herein reviewed.

debris, the atheroma. When the covering edge of the atheroma breaks, the lesion becomes an atheromatous ulcer. Simultaneously, calcification may occur and later even ossification. Injury to the lining surface of the blood vessels by atherosclerosis favors thrombosis, which increases the gravity of the lesions, especially, but not only, in the coronary arteries. Full descriptions of the gross and the microscopic changes in aortic and arterial tissues with atherosclerosis have been published by Marchand, Duff, Leary, Aschoff, Klotz, and Frei.[2]

A comprehensive understanding of the disorder should recognize that the changes in the smaller divisions of the arterial bed are similar, if not of the same appearance or dimension, as those more frequently seen in the aorta and its large branches and also that the fatty and fibrous plaques observed on occasion in the pulmonary artery, and even in the lining of veins such as the portal and others, belong in an over-all consideration of the same problem.

The Tissue Factor

The focal, rather than a diffuse distribution of the lipids in the lining of the aorta, has suggested to investigators that specific sites in the lining favor lipid infiltrations and that this selective lipid deposition could be due to a structural tissue factor at these loci. Duff [2] described fibrous thickenings in the human aorta just before the bifurcations, which, in theory, he related to an adaptive tissue response at the site of greater stress. Differences in the structure or defects of the internal elastic membrane of the aorta were correlated with these thickenings.

Rabbits and other animals have been used extensively in experimental studies of atherosclerosis. The aorta of rabbits fed cholesterol also has focal sites for lipid deposits. Because of this similarity and the easy access to the requirements for studies into the structure of the normal aorta, these tissue fundamentals have been investigated in the aorta of the rabbit. Duff, McMillan, and Ritchie [3] examined carefully the structure of the intima in the rabbit's aorta and found immediately caudal to most arterial ostiums a crescent-shaped fibrocytic thickening with its concavity directed cephalad. These mounds are thickest where they overhang the caudal edge of the ostium, and, curving away on each side, they merge gradually with the adjacent intima.

The intima of the rabbit's aorta has cells of four kinds: (1) the thin flat elongated plate-like endothelial cell, (2) the long and slender fibrocyte—the chief cellular constituent, (3) the much less frequent large phagocytic cell—the histiocyte, and (4) the scattered monocytoid cell resembling lymphocytes. The intima of the rabbit's aorta is covered by endothelium and is limited exteriorly by the internal elastic membrane. Between lies a loose connective tissue mesh, three or four layers deep in the arch but growing thinner distally until in the abdominal aorta the endothelium is separated from the internal elastic membrane by only a thin layer of cellular material.

The earliest atherosclerotic lesions (lipid deposits) observed by Duff, McMillan, and Ritchie in the aorta of rabbits fed cholesterol always were focal. There was no increase in the number of intima cells and no disorganization or modification of their arrangement. The only abnormality was the presence in the intima of droplets of lipids ranging in size from minute particles to 2μ. Most of the droplets were collected in clumps at the poles of the nuclei in the fibrocytes. They were also in the smaller number of histiocytes. The small lesions had 10 to 50 fibrocytes and a few histiocytes containing the lipid particles.

The deposits could be found in any part of the intima but were commoner in the thicker portions, with the larger content of the fibrocytes, such as in the arch and in the arterial mounds. The endothelium covering the lipid deposits and the media beneath did not appear abnormal. In the larger deposits, the number of fibrocytes

in the intima was always increased, probably through mitosis. Monocytoid cells and histiocytes accumulated in the center, forming a moderately well-demarcated core. The authors concluded that the lipids are not brought into the tissues by blood-borne phagocytes and probably even in the small deposits, the lipids in the intracellular droplets, entered the intima from the blood plasma.

Vascular surgery today affords isolated but significant examples of the tissue factor in the evolution of human atherosclerosis. A homologous aorta-tissue graft replacement of a coarctation stricture of the aorta, several years after the operation, had marked fatty deposits and even calcified plaques, whereas the lining of the host aortic tissues outside of the graft had none. Pathologists also are well acquainted with the fatty, fibrous, and even calcified plaques at the aortic end of the obliterated ductus Botalli when other portions of the lining of the aorta in adolescents and young adults are free.

Age in years, without the dynamic lipid factor, is not responsible for atherosclerosis. Necropsies of the bodies of the aged who, according to information from their associates, always have been spare, have enjoyed good health, and during their lifetime have engaged in hard physical work demonstrate aortas with a smooth lining and with only dilatation as the product of many years of function. In contrast, the aorta of an adolescent with chronic glomerulonephritis has atheromatous atherosclerosis as severe as that seen frequently in the aorta in middle adult life.

The Lipid Factor

Morphologic studies and chemical analyses of the human aorta have attempted to establish the significance of the lipids in atherosclerosis. The morphologic approach has emphasized the presence of lipids, especially of cholesterol, in the tissue lesions. Chemical analyses have revealed the composition of the lipids in the fatty and fibrous plaques and have provided data for comparisons with the composition of the lipids in the blood.

Published analyses of media tissues of the human aorta [6] without atherosclerosis indicate a progressive increase in all lipid fractions with age, but these changes have no obvious relation to the severity of the atherosclerotic lesions in the intima. Chemical analyses of the normal intima, while few, report a much higher lipid content than the corresponding media tissues.

Changes in Lipid Composition of Human Aorta with Atherosclerosis.—Quantitative analyses of the entire aorta with atherosclerosis have demonstrated a marked increase in the lipids. Schoenheimer, among the first to make such lipid analyses, concluded that the original lipids of the aorta are augmented in the development of atherosclerosis by a lipid mixture containing a constant proportion of free and total cholesterol. Kimmelstiel reported proportional increases of the lipid fractions present until atheromas formed. The lipid relations then changed and cholesterol increased rapidly in comparison with the other lipid fractions. Atherosclerotic aortas of nondiabetics, according to Lehnherr, contain increased amounts of lipids, with a greater proportion of total cholesterol, and those of diabetics have larger lipid deposits, but the quantitative relations of the fractions are similar.

These analyses of entire aortas did not differentiate between the chemical changes which may occur with advancing age and those due to the disease. This was emphasized by Meeker and Jobling, who obtained a better understanding of the chemical changes occurring with atherosclerosis of the aorta by analyzing the tissues of lesions separated from other tissues of the aorta and then compared these values with those of the unaffected tissues. As the lesions increased in severity, the proportion of cholesterol increased greatly, the increase being due largely to free cholesterol, and the ratio of free to bound cholesterol rose

TABLE 1.—*Average Values of Constituents of Intimal Lesions*

Type of Lesion	Moisture *	Lipid Extract †	Composition of Lipid Extract Corrected for Ash Content: Cholesterol ‡ Free	Cholesterol ‡ Ester	Phosphatide ‡ Ether-Soluble	Phosphatide ‡ Ether-Insoluble	Phosphatide ‡ Total	Galactoside ‡	Fatty Acids, Neutral Fat, Etc. ‡	Calcium †
Normal intima	71.6	14.4	14.2	38.6	13.7	6.4	20.1	8.0	19.1	0.23
Early fatty plaques	67.5	25.9	16.2	38.5	10.8	8.2	19.0	5.8	28.5	0.86
Fibrous plaques	66.5	27.2	18.1	47.5	5.9	9.0	14.9	4.5	15.0	3.94
Calcified tissues	38.6	12.8	21.9	47.2	3.9	9.3	13.2	4.6	13.1	24.3
Atheromatous ulcers	60.8	36.0	27.2	42.1	5.8	10.2	16.0	4.3	10.4	10.1

* The content is given as percentage of wet tissue.
† The content is given as percentage of dry tissue.
‡ The content is given as percentage of total lipid.

from 0.43 to 1.04 in the most advanced lesions. A later study, by Zeek, substantiated these results. The analyses of atherosclerotic plaques of the human aorta by Weinhouse and Hirsch [6] are reproduced in Table 1. These analyses demonstrated a progressive increase of the lipid content in the diseased tissues. In agreement with Meeker and Jobling, the ratio of free to combined cholesterol increases in the advanced lesions of atherosclerosis, along with an increase in both substances. The analyses also demonstrate a close agreement in the chemical composition of the lipids of the normal intima and of the fatty plaques, despite the larger amounts of total lipids in the latter.

The Deposition of the Lipids

Origin of the Lipids.—Determinations of the composition of the lipids in the normal human intima, in the lipid deposits, and in the fibrous and fatty plaques of the human aorta have added considerable support to the view that the tissue lipids are infiltrated from the plasma of the circulating blood. Page, Kirk, Lewis, Thompson, and Van Slyke [2] determined the free and total cholesterol, the phospholipids, and the neutral fats in the blood plasma of normal men of ages 20 to 101 years. The cerebrosides were not determined by these authors, and for comparison purposes this fraction was included in the neutral fat in the table of comparison published by Hirsch and Weinhouse.[2,6] The results given in Table 2 demonstrate a striking agreement between the two analyses, despite the differences in analytical procedures.

The close agreement in composition between the lipid extracted from the plasma and that in the normal intima and the wide differences between the lipid extracts from the latter and those from the media indicate that the lipids of the intima originate in the plasma rather than in the protoplasm of the cells. The comparison also supports the validity of the opinion that the intima is permeable to the lipids of the plasma and that the intima has no selective action on these lipids, a conclusion that has been expressed by others.

The fatty acid content of the total lipids and cholesterol esters of normal human plasma and of atheromatous plaques of the human aorta was reported recently by Tuna, Reckers and Frantz.[20] They used some of

TABLE 2.—*Comparison of Lipid Composition of Blood Plasma and Arterial Tissue*

	Blood Plasma *	Intima *	Early Plaques *	Media *
Free cholesterol	14.1	14.2	16.2	17.3
Cholesterol esters	38.3	38.6	38.5	16.7
Phospholipids	22.8	20.1	19.0	34.1
Neutral fat, etc.	23.3	27.1	26.3	31.9

* The values are given as percentages of total lipid.

the newer methods for lipid analysis. No qualitative or gross quantitative differences between the total fatty acids of the normal plasma and of the atheromatous plaques were found excepting slight unexplainable differences in the linoleic and oleic acid content of the cholesterol esters. Their results were interpreted as support for the opinion that the plaques are formed by infiltration and indiscriminate deposition of the blood lipids in the arterial wall.

The animal experimentors, advocating the synthesis of the lipids in situ by the aortic tissues as the mechanism by which the fatty plaques are formed in the intima, would need to explain (1) the focal distribution of this synthetic process, (2) the synthesis of a mixture of several lipids with a chemical composition similar to that of the blood, even to the content of the lipochrome, and (3) why the media of human arterial tissues has a lower content of lipids, as well as a different lipid composition, than has the intima.

The close agreement between the composition of the lipid extracts from the normal human intima and that of the lipids in the early fatty deposits suggests further that the latter arise by a nonspecific deposition of the plasma lipids. The changes in lipid composition which occur in the late stages of the lesions, such as the reversal of the cholesterol ester to free cholesterol ratio, may result from several processes, such as phagocytosis, other tissue reactions against lipid substances and their products, and necrosis but especially from chemical changes in the composition of the lipids deposited. These processes, however, including those of calcification and ossification, are secondary to the initial deposition of the lipids.

Lipids of the Human Blood.—Reports on the lipid content of human plasma, as a rule, record the results of sampling at a fasting level. These analyses express the amounts of the blood lipids "in transport" at the time the samples were taken. Page, Kirk, Lewis, Thompson, and Van Slyke observed no significant changes in any lipid fraction from youth to old age. When the total lipids of the plasma increased, the free and ester cholesterol, the phosphatids, and the neutral fats participated but not to the same extent. Free cholesterol changed the least and neutral fat the most.

The number of reports on analyses of the cholesterol content of the human blood serum in local and world-wide surveys, in the diagnosis and the treatment of patients, and in animals used for experiments is comparable with the number of trees in a forest. The first systems published for the microanalysis of the blood constituents included directives for the determination of the serum cholesterol, a procedure which is essentially the same today as when it was published in 1919. The upsurge in ascribing to cholesterol, especially that of the diet, a specific causal relationship to human atherosclerosis came when the aorta of rabbits and other animals fed diets containing large quantities of added cholesterol were found to have lipid deposits resembling those observed in human aortas with atherosclerosis. Without an attempt to review the enormous number of published reports, the following statement by Ancel Keys [1] is quoted: "Unwarranted inferences have been made from cholesterol feeding experiments with animals. The evidence—both from experiments and field surveys—indicates that the cholesterol content, *per se*, of all natural diets has *no* significant effect on either the serum cholesterol level or on the development of atherosclerosis in *man*." Apparently many, if not most, cases of atherosclerosis in man are not associated with appreciable hypercholesteremia, and there seems to be no doubt that the disease may develop without recognized abnormality of the blood lipids. We should be mindful, however, that a normal level of the blood lipids and of their fractions has not been established for man which would serve as a standard of reference for all geographic groups.

Clinical evidence favors the view that a real hyperlipemia is a factor in atherosclerosis. The close association between high

blood cholesterol levels and atherosclerosis in diabetes has been emphasized and also the high incidence of atherosclerosis in systemic xanthomatosis, a metabolic disorder associated with hypercholesteremia.

Physical Distribution of Lipids in Blood.—Particles of lipid 0.5μ to 1μ (or larger) in diameter are in transport in the blood. Variations in the size of these particles, but not the factors concerned with this physical distribution, have been emphasized by Gofman in human atherosclerosis. Much of the lipid absorbed from the bowel reaches the blood as an emulsion and is utilized by the tissues or is stored in the fat depots. A lipemia results when the lipid particles in the blood exceed the levels considered normal. Ludlum, Taft, and Nugent[2] believed that the particles of lipid in the blood are stabilized by a protein film because the first zone of aggregation of the particles occurred at a pH range of 4.7 to 5.3, approximately the isoelectric points of albumin and globulin. The droplets coalesced when the acidity was sufficient to precipitate the protein and to destroy the film. The membrane about globules of fat in milk, according to Palmer and Wiese,[2] is a mixture of protein and phospholipid.

The term "lipoproteins" of the blood is used freely in clinical medicine as though it were a definite chemical substance, especially in electrophoresis studies of serums. Lehninger[1] has stated that considerable support can be marshaled for the view that virtually all lipids normally found in the tissues and body fluids exist in the form of lipoproteins or lipid-protein complexes. This implies that there are many different types of lipoproteins.

The composition of the emulsified lipid can be significant in stabilization of an emulsion, and the degree of dispersion of lipids seems important in determining how the tissues utilize or dispose of a lipid complex—the smaller particles being engulfed by tissue phagocytes, the larger masses, by reduction through an encapsulation by granulation tissues.

Site of Lipid Deposits in Aorta.—Opinions differ as to whether the lipid particles deposited in the intima are intracellular primarily and later become extracellular with necrosis of the cells or are extracellular at first and then intracellular. Morphologic studies of human tissues are controversial. Duff, McMillan, and Ritchie found in rabbit tissues with experimental atherosclerosis that the earliest fatty deposits consisted of a few fibrocytes with fat droplets. In all fatty deposits the lipid particles were mostly, if not entirely, intracellular. If one is mindful that the lipids of the blood are transported in the form of small particles and that the normal intima and the simple lipid deposits in the initial phase of atherosclerosis have a composition corresponding to that of the lipids of the blood, much of the reason for argument in this controversy disappears.

Tissue Reactions Caused by Lipids.—Lipids deposited in tissues stimulate inflammatory reactions whose tissue products eventually are reduced to fibrous granulation tissue plaques. The various lipids in the deposits contribute to the total tissue reactions. Among these lipids the fatty acids, rather than cholesterol, seem to have the greatest irritative properties. The fatty acid composition of atheromatous lesions, according to McArthur,[7,8] is stearic 2.9%, palmitic 14.6%, oleic and some other highly unsaturated acids 65.2%, linoleic 9.4%, arachidonic 2.1%, and petroleum-insoluble acids 5.8%. Cholesterol, itself, when introduced into tissues produces a focal foreign-body giant-cell granuloma. The acicular slits commonly observed in granulomatous atherosclerotic plaques in the human aorta, and in other granulation tissues of the human body, especially with an old hemorrhage, are associated with these foreign-body giant cells.

The changes of cholesterol esters (60% to 70% of the total) in lipid deposits releases fatty acids and free cholesterol. The acicular slits observed in the lipid deposits of atherosclerotic plaques are ascribed to cholesterol crystals dissolved in the prepara-

tion of the sections. The separation of a crystalline product such as cholesterol in tissues probably is according to the generally accepted laws of crystallization of a solvent saturated with a solute. Chemical analyses of the advanced atherosclerotic plaques demonstrate a shift of the ratio of free to total of from 0.43 to 1.04. This shift in ratio may result from a cleavage of the ester compounds and the accumulation of the free cholesterol in the lipid mixture—the saturation by a lipid solute of a lipid solvent.

Variations in Amount and Composition of Lipids of Human Serum

The Hyperlipemias.—The simplicity of the procedure for the estimation of the cholesterol content of the serum in small samples of blood, in contrast with the more complicated procedures required and the larger amounts of blood needed for the quantitative determinations of the other lipid constituents, is probably the main reason why so much has been published on the cholesterol content of the blood in health and disease. The level of cholesterol in the blood has been assumed by some to be a fairly accurate measure of the total lipid content, despite published statements to the contrary. A colorimetric method for estimating the total esterified fatty acids in small samples of serum was devised in the laboratory at St. Luke's Hospital.[9,10] Although this procedure gave significant information of the lipids of the blood, the distribution of the esterified fatty acids in the neutral fat, in the phospholipid, and in the cholesterol-ester fractions was found to be much more important. The methods for lipid analyses of the blood in small samples were extended to obtain these values.

The total esterified fatty acids in the serums of 102 healthy young adults at the fasting level ranged between 7.0 and 12.6, with a mean of 9.2 mEq. per liter.[11] Following a test meal of 2 to 3 gm. of fat per kilogram of body weight the total esterified fatty acids of the blood among 21 young adults increased over the initial fasting level between 25% and 146%.[12] The cholesterol content of the blood during this postprandial hyperlipemia did not change significantly. In many tests, the peak level of the postprandial hyperlipemia was attained by the third or fourth hour after the meal and then the lipids declined but even after seven hours had not returned to the original value.

The total esterified fatty acids in the serum lipids of diabetics under control and at the fasting level was found to range in the high normal values.[12] When the diabetic was given the test meal, the esterified fatty acids of the blood rose quickly to a much higher level than occurred in the nondiabetic, and the duration of this hyperlipemia was much more prolonged. The cholesterol content of the blood changed very little. Other studies of the lipids and the sugar of the blood in diabetics disclosed a parallel relationship between the hyperglycemia and the hyperlipemia.[13] The composition of the lipids in diabetic hyperlipemia are given herewith for a patient brought to the hospital in coma. His blood sugar when he was admitted in coma was 600 mg. %; the level of total esterified fatty acids of the serum was 98 mEq. per liter, of which 75 mEq. per liter, or 76%, was in the neutral fat fraction; 15 mEq. per liter, or 15.5%, was in the phospholipids, and 8 mEq. per liter, or 8%, was in the cholesterol ester fraction (62% of the total cholesterol). Several days later, when the sugar of the blood had dropped to 112 mg. %, the level of total esterified fatty acids of the serum was 14 mEq. per liter, of which 8 mEq., or 57%, was in the neutral fats; 4 mEq., or 30%, was in the phospholipids, and 2 mEq., or 14%, was in the cholesterol esters (60% of total). These results emphasize that when the diabetic is hyperglycemic he is also hyperlipemic and also that his postprandial hyperlipemia with a fat test meal is much greater and more prolonged than occurs in the nondiabetic. All main fractions of the blood lipids during this hyperlipemia increase, but the increase of the neutral fats is much greater than of the others. Atherosclerosis,

vascular retinopathy and glomerulosclerosis of the kidneys are known to occur much more frequently in the diabetic than in the nondiabetic.

The serum with idiopathic hyperlipemia [14] also has a marked elevation of the total esterified fatty acids, of which a large increase is in the neutral fat and much smaller increases are in the phospholipid and the cholesterol fractions. With diet restriction, the lipids of the blood may drop to near the upper normal range and the greatest decrease is in the neutral fat fraction.

Hyperlipemia occurs also with recognized disorders of lipid metabolism, such as xanthomatosis, and in nephritis, notably in the nephroses, but the composition of the lipids in these disorders is not the same; in the xanthomatoses the cholesterol fraction is high, and in the nephroses the neutral fat is high.

Experimental Atherosclerosis.—Rabbits, rats, guinea pigs, dogs, monkeys, and chickens have been used in experiments to determine the factors responsible for the evolution of atherosclerosis and how this vascular disorder can be prevented or modified. Fed a diet to which cholesterol is added, but with some variations among the species, these animals become hyperlipemic, and lipids with a high content of cholesterol are deposited in the lining of the aorta and of the arteries and in the reticuloendothelial cells of many other tissues of the body, including the spleen and the liver. Because the atherosclerotic lesions of the aorta and its branches occur in these animals when fed cholesterol, dietary cholesterol has been emphasized as the causal factor in the evolution of human atherosclerosis. Objectors to this broad implication remind the experimenters that rabbits absorb cholesterol from the intestinal tract in amounts far greater than the animal tissues are able to metabolize. The objectors also emphasize that the hyperlipemia developing in animals fed thus is an unstable emulsion and that these lipids, probably on the basis of their chemical composition, are engulfed by phagocytic cells in the lining of the blood vessels and in other tissues where depositions occur. The deposition and phagocytosis of the emulsified lipids in the various sites mentioned seems to be related to the high content of the cholesterol in the lipid complex of the dispersed particles. Analyses of the hyperlipemic serum of rabbits fed cholesterol [15] demonstrate a total serum lipid increase of sixteenfold over the normal, with a twenty-five-fold increase of the free cholesterol, a thirtyfold increase of the cholesterol esters, a sevenfold increase of the phospholipids, and a fivefold increase of the neutral fats. Clearly, in this disproportionate increase among the lipid fractions, the increase of the free and the ester cholesterol fractions greatly exceeds the elevation of the phospholipids and of the neutral fat. The experimenters should realize that in these experimental studies of atherosclerosis they are, in fact, testing a lipid factor, namely, a hyperlipemia, and have given scant thought to the significance of the composition of the lipids of the blood in their experiments.

The lipids of the blood are transported in the plasma as emulsified particles of mixed chemical composition and for practical purposes consist of three main classes: (1) the neutral fats, namely, the triglycerides of the saturated and unsaturated fatty acids, (2) the sterols (cholesterol) and their ester derivatives, and (3) the phosphatides, such as the cerebrosides and the ceramides. The neutral fats and the phosphatides are closely related chemically, the latter having one of three fatty acids of a triglyceride fat replaced by a choline or cholamine phosphoric acid radicle.

The composition of the emulsified lipids in the blood at the fasting level and in the various forms of hyperlipemia can be likened to a solvent and its solutes in varying proportions. At the one extreme the solvent is in excess, as with the simple postprandial hyperlipemia, the early phases of idiopathic hyperlipemia, most forms of diabetic hyperlipemia, and some of the lipemias associated with nephritis in the

human (nephroses) or produced experimentally in animals. At the other extreme, the solutes approach the supernaturation level, as in the feeding of cholesterol to rabbits and other animals with the production of atherosclerosis and in diabetics or other patients with xanthomatosis. The lipid imbalance when the solute is in excess within a short time results in the deposition of lipids containing large amounts of cholesterol in the lining of the aorta and in many other tissues of the body.

Rabbits on a regular diet supplemented by 15 to 50 cc. of 36% cream daily by gavage became hyperlipemic.[16] The serum lipids had a high content of neutral fats and phospholipids, while the total cholesterol (approximately 70% ester) increased only severalfold. After six months of this regimen, when killed the animals had no atherosclerosis of the aorta and arteries and no significant lipid deposits in the tissues. If the hyperlipemia in these rabbits exceeded a level of about 30 mEq. per liter the animals had an acute metabolic disorder and died. At this stage there was a sudden marked elevation of the blood lipids, especially of the neutral fat fraction, and also a hyperglycemia.

The hyperlipemia of rabbits fed cholesterol,[17,18] in contrast, reaches a much higher level than that of rabbits fed cream. Large amounts of lipids with the hyperlipemia of the cholesterol-fed group are deposited in the tissue phagocytes and in plaques in the lining of the aorta and arteries. The blood lipids of these cholesterol-fed rabbits have a disproportionate high content of total cholesterol (70% to 75% ester), in contrast with the blood lipids in the hyperlipemia of the cream-fed rabbits, with a high content of the neutral fat fraction. The rabbits fed cholesterol with this form of hyperlipemia do not have an acute metabolic disorder despite the much greater elevation of the blood lipids. Instead they have a wasting disorder with extensive deposits of the lipids in many tissues of the body. If, for the purpose of comparison of the blood lipid composition, the esterified fatty acids in the neutral fat and in the phospholipid fractions (solvents) together are placed in a ratio with those in the cholesterol ester and the equivalent free cholesterol fractions (solutes), a difference in relations is demonstrated for the two kinds of hyperlipemias.

$$\text{Esterified fatty acids} \frac{\text{neutral fats} + \text{phospholipids}}{\text{cholesterol ester} + \text{free cholesterol (calculated)}}$$

The blood lipids of the hyperlipemia with cream only have a high content of the solvent fats (2 to 3.3:1), a ratio which is at or above the ratio expressing the original normal value. The hyperlipemia with blood lipids of this composition is not associated with lipid deposits in tissue phagocytes or in the lining of blood vessels. The much greater hyperlipemia in the rabbits fed cholesterol with a pellet diet is associated with extensive lipid deposits in tissue phagocytes and in plaques of the lining of the aorta and arteries. The ratio of solvent to solute in the composition of the serum lipids with this hyperlipemia is much below a 1:1 ratio (0.7 to 0.4:1). Lipids with this composition in the tissues of the host apparently have the physical properties of a particulate substance which stimulates phagocytosis (lipophages) and accumulate in the phagocytic cells in the blood vessels and many other tissues of the body. The experimental studies with macromolecular substances[19] such as polyvinyl alcohol and methylcellulose align themselves with this form of hyperlipemia in animals.

Analyses of the lipids in the aortic plaques of the rabbits fed cholesterol[17,18] disclose that the plaques are a mixture of lipids, which reflects the fractional composition of the blood lipids. Each lipid fraction in the plaques is increased manyfold over the corresponding fraction of the plasma lipids, with the possible exception of the neutral fat. Changes in the composition of the lipids after deposition whereby the solute is relatively increased or the solvent is decreased can augment an initial solvent-solute disproportion. A shift in the distribu-

tion of the cholesterol from the ester to the free form in the lipid deposits can contribute to this disparity.

Comment

This analysis of the causal factors of atherosclerosis leads to the opinion that two basic factors, a tissue and a lipid, conjoin to produce the initial lipid deposits in the intima of the aorta and arteries. An interaction of these two factors results in the fatty plaques of the intima, the recognized initial phase of the disorder. The infiltrated lipids, according to the present evidence, enter the tissues of the intima from the circulating blood stream. A tissue medium suitable for deposition is necessary and, according to anatomic studies, is a natural constituent of the intima of even the so-called normal aorta. These sites of deposit, by the original structure of their tissues, are focal; with disease they become more diffuse. The lipids in transport in the serum may range (1) in amounts and (2) in chemical composition. Were conditions suitable to subject the human aorta to anatomic studies when the circulating blood is hypo- or normolipemic and again when it is hyperlipemic, as has been done in animals, the details of establishing the contributions by each factor, the tissue, and the lipid, with their conjoined effects, could be established more directly. However, fibrocytes and mononuclear phagocytes in the intima of all animal species probably have the common property of engulfing lipid particles infiltrated from the blood plasma.

Rabbits fed a balanced diet to which cholesterol is added soon become hyperlipemic. The earliest lipid deposits observed in the intima of these animals during the initial stages of the hyperlipemia are in the thicker portions with a larger normal content of fibrocytes. As the plaques increase in size they have a greater content of fibrocytes and mononuclear phagocytes with the engulfed lipid particles. The lipid factor in this experimental hyperlipemia in rabbits is dynamic; the latent tissue factor is respondent through cell mitosis. The chemical composition of the blood lipids in this hyperlipemia induced in animals by cholesterol added to the food is significant because the reticuloendothelial cells in many tissues of the body react to the emulsified lipid particles as they do to a finely divided or emulsified foreign substance. Chemical analysis demonstrates that the plasma lipids of the cholesterol-fed rabbits have a disproportionate high content of esterified and free cholesterol, although the normal ratio is maintained. In contrast with this induced hyperlipemia, the hyperlipemia of rabbits fed cream is not associated with atherosclerotic plaques or with appreciable deposits of lipids in the tissue phagocytes. The lipids of the blood in the hyperlipemia produced by feeding cream have a high proportional content of the neutral fats and phospholipids (solvent) and a small proportional content of cholesterol (solute), even though each fraction of the blood lipids including cholesterol is increased over the normal.

These differences in lipid behavior in the two forms of hyperlipemia emphasize that the composition of the circulating lipids of the blood is significant in producing lipid deposits in intima tissues which even naturally are susceptible to deposition. The behavior of the two lipid systems in the tissues can reflect also the simple fact that the one mixture of lipids is rapidly utilized by the tissues, while the other mixture of lipids is not and has residue effects in the tissues of the host.

Chemical analyses of the lipid deposition of the human aorta and of the rabbit aorta demonstrate that the plaques are mixtures of the three main groups of tissue lipids—the neutral fats, the phospholipids, and cholesterol—and that these mixtures reflect the composition of the lipids of the circulating blood. The results of these analyses further support the conclusion that the lipids in the deposits are derived from lipids in transport in the blood. The emulsified lipids of the blood during the postprandial phase of diges-

TABLE 3.—*Composition of Blood Lipids in Transport when Food Intake is Obstructed*

Date	Total Esterified Fatty Acids	Cholesterol				Phospholipids		Neutral Fat (Esterified Fatty Acids) mEq/L.	Sugar Mg. %	NPN Mg. %
		Total	Free, Mg. %	Ester	Esterified Fatty Acids, mEq/L.	Mg. %	Esterified Fatty Acids, mEq/L.			
9-27-54 *	18.5	163	58	105	2.71	7.82	4.55	11.24	84	
10- 5-54	12.7	147	55	92	2.37	7.5	4.36	5.97	79	48
10-12-54	12.4	115	30	85	2.2	9.64	5.61	4.89	79	
10-19-54	8.17	93	30	63	1.63	8.25	4.8	1.74	43	
10-26-54	3.42	98	34	64	1.65	3.06	1.8	0.0	47	43
Death 10-30-54										

* This patient was unable to take food by mouth because of a high intestinal obstruction due to generalized carcinoma of the peritoneum. Fluids, salts, dextrose, and amino acids were given intravenously, but no fats.

tion reflect the lipid content of the ingested food; those during starvation, the lipids in transport from the storage depots to the tissue cells. The lipids of the blood in the postprandial phase have a high neutral fat fraction. The composition of the blood lipids in transport when food intake is obstructed by disease or during starvation is illustrated in Table 3.

Realization that a so-called normal intima, because of inherent differences in tissue structure, has susceptible foci for lipid deposition and that these lipids are derived from lipids in transport in the blood plasma gives dynamic significance to the lipid factor. A large number of estimations of cholesterol in the serum have been made with blood at the so-called "fasting level." Keys' published comparisons of blood cholesterol in relation to the incidence of atherosclerosis between populations in many different parts of the world have meaning. Populations with an average high value of serum cholesterol are likely to have a high total lipid content of the blood, and populations with an average low value of cholesterol would have an associated low total lipid content of the blood. An increase of the total blood lipids with disease, except in xanthomatosis or similar metabolic disorder of lipid metabolism, is usually associated with a much greater increase of the neutral fat and phospholipid fractions than in the cholesterol. Is it possible that even this increase in the cholesterol fraction is only part of a total lipid compensating mechanism?

Most of the studies of atherosclerosis induced in animals with food containing added cholesterol are actually investigations of the lipid factor with a specific form of hyperlipemia. The fractional composition of the lipids of the blood in this hyperlipemia has not been determined in most of the experiments. The attention of the investigators has been focused on the markedly elevated total cholesterol and the ratio of the ester to the free fractions. Had the experimenters realized that both the blood lipids and the atherosclerotic plaques in the aorta are lipid mixtures, those in the plaques reflecting the composition of those in the blood, and also that these quantitative lipid relations in the hyperlipemic animal are entirely different from those in the human, there would have been much less enthusiasm in transferring animal-tissue observations with all of their implications into the interpretations of human atherosclerosis.

Chemical changes occur in the lipids of the human aortic plaques and in the lipid deposits in the tissues of animals used in experiments. Crystals of cholesterol (acicular slits in tissues) separate from the lipid mixture, and multinucleated foreign-body giant cells form along the edge of the crystals. Most of the investigations of the effects of the lipid mixture on tissues have gone no further than to stress the presence of cho-

lesterol, with the implication that it is the main noxious agent.

General pathology and experimental pathology have a large amount of information concerning tissue injuries, granulomas, and scars caused by fats and their fatty acid derivatives. This analysis suggests that more appreciation be given to the effects in arterial tissues of the fatty acid derivatives of the lipid deposits, rather than of cholesterol as such, in the evolution of the lesions of atherosclerosis beyond the initial fatty deposits of the lining.

St. Luke's Hospital, 1439 S. Michigan Ave. (5).

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News and Comment

GENERAL NEWS

Commissioned Officer Student Training and Extern.—One hundred thirty-five medical, dental, engineering, science, nurse, and veterinary students from 120 approved four-year professional schools have spent the summer months in U. S. Public Health Service facilities under the year-round training program of the Service.

The program is known as COSTEP, for Commissioned Officer Student Training and Extern Program. Assignments under COSTEP are open each year to medical, dental, engineering, science, nurse, and veterinary students who complete either their second or third year of professional education on or before July 1 and who are interested in becoming Reserve Officers in the Commissioned Corps of the Service.

Students selected for COSTEP are offered commissions in grades equivalent to those held by officers in the Armed Forces. They are then placed on active duty for a period not to exceed 120 days. Opportunities for either medical or dental internships or active duty upon graduation are also available to qualified students.

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The nature and location of assignments under COSTEP are, in general, as follows:

1. Laboratory assignments in medical research programs at the National Institutes of Health, Bethesda, Md., and the Communicable Disease Center, Atlanta, Ga.

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The competing essays may cover either clinical or research investigations, should not exceed 3000 words in length, and must be presented in English. Duplicate typewritten copies, double-spaced, should be sent to the Secretary, Dr. John C. McClintock, 149½ Washington Ave., Albany 10, N. Y., not later than Jan. 15, 1959. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

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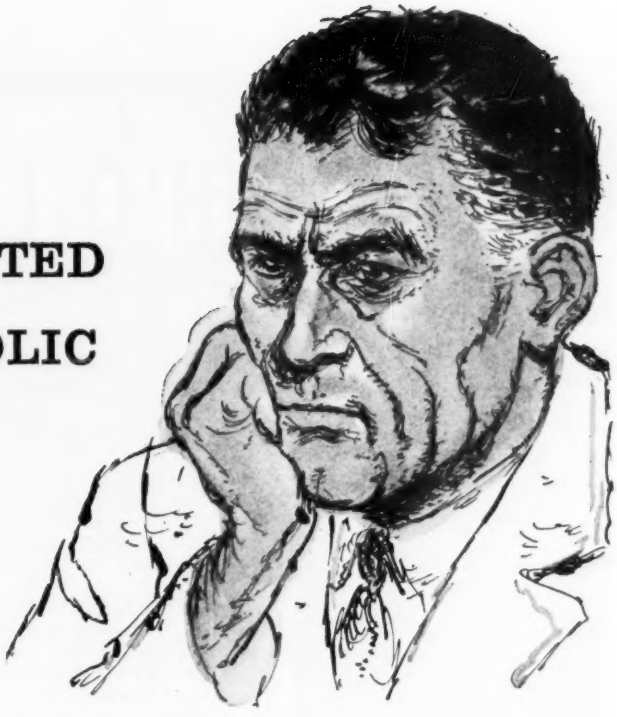

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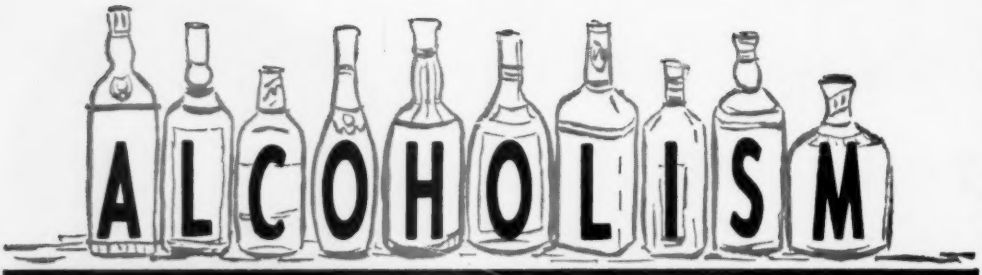

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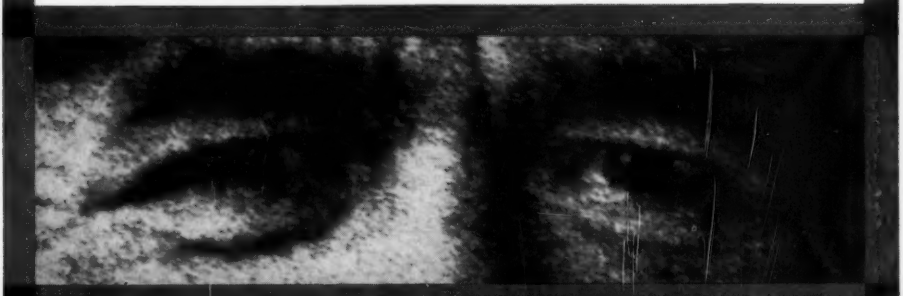

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Source—Hyman, M.: Some Aspects of Psychiatry in General Practice, GP *16*:83 (Oct.) 1957.

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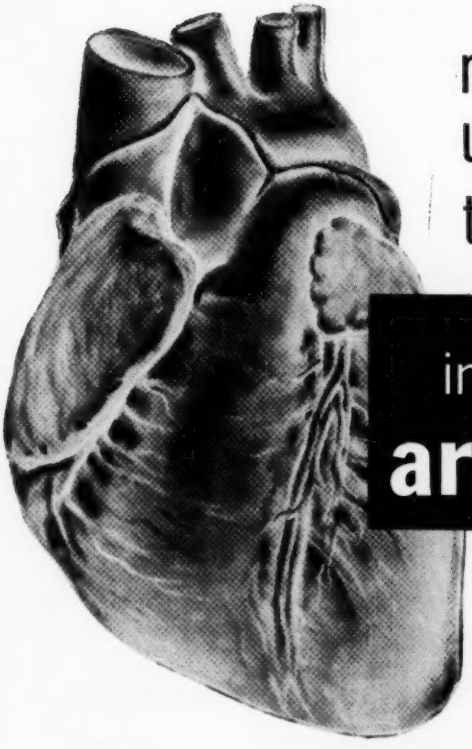

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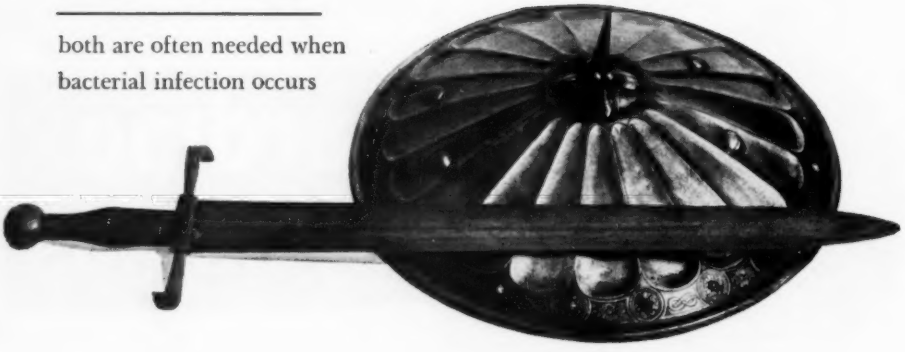

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